TREATMENT OF ATOPIC DERMATITIS

Related Applications

This application claims the benefit of Great Britain Priority Application Nos. GB 2111492.1, filed on August 10, 2021, GB 2115152.7, filed on October 21, 2021, GB 2204211.3, filed on March 24, 2022, and GB 2204291.5, filed on March 25, 2022, the contents of which are incorporated herein by reference in their entireties for all purposes.

Background

Atopic dermatitis (AD) is the most common type of eczema, affecting more than 9.6 million children and about 16.5 million adults in the United States. It is a chronic condition that can come and go for years or throughout life, and can overlap with other types of eczema.

In people with AD, the immune system becomes disordered and overactive. This triggers inflammation that damages the skin barrier, leaving it dry and prone to itching and rashes that may appear purple, brown or grayish hue in darker skin tones and red in lighter skin tones.

Research shows that some people with eczema, especially atopic dermatitis, have a mutation of the gene responsible for creating filaggrin. Filaggrin is a protein that helps our bodies maintain a healthy, protective barrier on the very top layer of the skin. Without enough filaggrin to build a strong skin barrier, moisture can escape and bacteria, viruses and more can enter. This is why many people with AD have very dry and infection-prone skin.

Itching is the hallmark of AD, with some data showing that more than 85% of people with the condition experience this distressing symptom every day. Sore or painful skin and poor sleep caused by itching are also common.

People with AD can get rashes anywhere on the body that can ooze, weep fluid and bleed when scratched, making skin vulnerable to infection. Skin can become dry and discoloured, and repeated scratching can cause thickening and hardening — a process called lichenification. Although AD can affect any part of the body, it most often affects the hands, insides of the elbows, backs of the knees and the face and scalp in children.

Atopic dermatitis typically begins in childhood, usually in the first six months of a baby's life. Even though it's a common form of eczema, it's also severe and long-lasting. When you or your child have atopic dermatitis, it may improve at times; but at other times, it may get worse. In some children, symptoms may taper off as they grow up, while other children will have atopic dermatitis flares into adulthood.

Atopic dermatitis exists with two other allergic conditions: asthma and hay fever (allergic rhinitis). People who have asthma and/or hay fever or who have family members who do, are more likely to develop AD.

There is currently no cure for AD, but depending on the severity of AD, treatments include lifestyle changes, over-the-counter (OTC) remedies or prescription medication.

The main treatments for AD are:

- emollients (moisturisers) – used every day to stop the skin becoming dry, and
- topical corticosteroids – creams and ointments used to reduce swelling and redness during flare-ups

Other treatments include:

- topical pimecrolimus or tacrolimus for eczema in sensitive sites not responding to simpler treatment
- antihistamines for severe itching
- bandages or special body suits to allow the body to heal underneath
- DUPIXENT (dupilumab) is indicated for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. As described for example by Tubau et al., Immunotherapy 13:327-344, 2021, dupilumab, which is currently the only approved mAb for AD treatment, blocks IL-13 but also IL-4 by inhibiting the IL-4Rα1 subunit of their common receptor. It is highly effective, with an excellent safety profile, even though a significant proportion of patients develop dry eyes and/or blepharoconjunctivitis that complicate their management.
- Pipeline products include JAK inhibitors, IL-13 inhibitors and IL-31 inhibitors. However, JAK inhibitors are associated with safety concerns (e.g., black-box warning) and Anti-IL-31 shows poorer efficacy.

OX40 ligand (OX40L) is a TNF family member; a 34 kDa type II transmembrane protein. The crystallized complex of human OX40 and OX40L is a trimeric configuration of one OX40L (trimer) and three OX40 monomers. The human extracellular domain is 42% homologous to mouse OX40L.

OX40L is not constitutively expressed but can be induced on professional APCs such as B-cells, dendritic cells (DCs) and macrophages. Other cell types such as Langerhans cells, endothelial cells, smooth muscle cells, mast cells and natural killer (NK) cells can be induced to express OX40L. T-cells can also express OX40L. The OX40L receptor, OX40, is expressed on activated T-cells ($CD4^+$ and $CD8^+$ T-cells, Th2, Th1 and Th17 cells) and $CD4^+Foxp3^+$ cells, even in the absence of activation.

The interaction between OX40 and OX40L occurs during the T-cell–DC interaction 2 or 3 days after antigen recognition. After leaving DCs, the OX40-expressing T-cell may interact with an OX40L-expressing cell other than a DC and receive an OX40 signal from this cell, which may provide essential signals for the generation of memory T-cells, the enhancement of Th2 response and the prolongation of the inflammatory responses. OX40 signals into responder T-cells render them resistant to Treg mediated suppression.

WO2015/132580, WO2016/139482 and WO2018/083248 describe anti-human OX40L (hOX40L) antibodies and fragments and medical applications for treating or preventing hOX40L-mediated diseases or conditions in humans.

Summary

In some embodiments is provided a treatment targeting an upstream OX40L dependent pathway, to be effective in treating inflammatory diseases or disorders, immune-mediated diseases or disorders, inflammatory skin diseases or disorders. Some embodiments provide a treatment targeting an upstream OX40L dependent pathway, to be effective in treating both acute and chronic AD. The treatment is associated with an attractive dosing frequency, a low-volume induction and maintenance regime and strong efficacy and safety profiles. Advantages of formulations for subcutaneous administration include being more patient-friendly, as it may be administered by the patient at home, and an inconvenient physician visit can thus be avoided. Also, administration times may shortened, which is beneficial for patients and healthcare providers. Some embodiments also provide reduced needle burden, i.e., a reduced number of injections per year, which will result in potentially improved compliance and thus patient outcomes. Some embodiments also provide treatments with surprisingly consistent pharmacokinetic (PK) parameter estimates in IV and subcutaneous population PK models, which are not meaningfully impacted by anti-drug antibodies, which is especially surprising for subcutaneous administration. To this end, some embodiments provide:

In a first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 2 to 6 months.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 6 months.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration EASI score is reduced at least 10% relative to a baseline EASI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration vIGA-AD score is reduced at least 10% relative to a baseline vIGA-AD score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration IGA-AD score is reduced at least 10% relative to a baseline IGA-AD score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration BSA score is reduced at least 10% relative to a baseline BSA score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration SCORAD index is reduced at least 10% relative to a baseline SCORAD index.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration PO-SCORAD index is reduced at least 10% relative to a baseline PO-SCORAD index.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration DQLI score is reduced at least 10% relative to a baseline DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the subject is a chronic Atopic Dermatitis patient.

In a second configuration, there is provided a glass vial containing an anti-OX40L antibody, or antigen-binding fragment thereof.

In a third configuration, there is provided a prefilled syringe containing an anti-OX40L antibody, or antigen-binding fragment thereof.

In a fourth configuration, there is provided a microinfusor containing an anti-OX40L antibody, or antigen-binding fragment thereof.

In a fifth configuration, there is provided a pen delivery device containing an anti-OX40L antibody, or antigen-binding fragment thereof.

In a sixth configuration, there is provided an autoinjector delivery device containing an anti-OX40L antibody, or antigen-binding fragment thereof.

In an seventh configuration, there is provided a kit comprising a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device or autoinjector according to any of the third to sixth configurations; and a label and/or instructions specifying administration in accordance with a method of the first configuration.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating Atopic Dermatitis in accordance with a method of the first configuration.

In a further configuration, there is provided a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit according to any one of the second to seventh configurations, for use in a method of treating Atopic Dermatitis in accordance with a method of the first configuration.

In a further configuration, there is provided the use of an anti-OX40L antibody, or antigen-binding fragment thereof, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with a method of the first configuration.

In a further configuration, there is provided the use of a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit according to any one of third to eighth configurations, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with a method of the first configuration.

In a further configuration, there is provided a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a

therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via subcutaneous injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via subcutaneous injection.

In another configuration, there is provided a method of treating atopic dermatitis in a subject, the method comprising selecting a subject having atopic dermatitis, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody or antigen-binding fragment thereof, wherein the anti-OX40L antibody or antigen-binding fragment thereof comprises heavy chain complementarity regions (HCDRs) of SEQ ID NOs: 42, 44 and 46, and light chain complementarity determining regions (LCDRs) of SEQ ID NOs: 56, 58 and 60.

References to the first configuration as used herein include the "first configuration" and any "alternative statement of the first configuration". The features of any statement of the first configuration may read in combination with any of the second and subsequent configurations of the invention.

Brief Description of Figures

FIG. 1 graphically depicts the overview of study design of Example 1. Healthy volunteers in Cohorts 1 to 3 received a single I.V. infusion of KY1005 (0.006, 0.018 or 0.05 mg/kg) or placebo, with blood samples taken up to Day 113. Cohorts 4 to 8 received an initial loading dose on Day 1 (0.15, 0.45, 1.35, 4.0 or 12 mg/kg), and two maintenance doses (50% of the loading dose), administered on Days 29 and 57.

FIG. 2A-B graphically depict percentage change in anti-tetanus toxoid (TT) IgG and IgM titer versus placebo at Day 85, Cohorts 4 to 8 (95% CI) adjusted for baseline variability. Immunization with recall antigen, tetanus toxoid (TT), resulted in a humoral (IgM and IgG) response in all who were immunized. No observable effect of KY1005 on mean anti-TT IgG levels (**FIG. 2A**) were observed

although anti-TT IgM (**FIG. 2B**) suppression was numerically greater than placebo in all treatment arms but not dose dependent.

FIG. 3 graphically depicts the overview of study design of Example 2. Patients underwent Day 1/baseline assessments and were randomized in a 1:1:1 ratio to receive an intravenous (I.V.) injection of KY1005 at a low (200 mg) or high (500 mg) dose, followed by three maintenance doses at 50% of the loading dose at 28-day intervals on Days 29, 57 and 85, or matching placebo.

FIG. 4 graphically depicts percentage change in EASI score from baseline over time illustrated using LSM with 95% confidence interval (CI). Reductions in EASI score from baseline to Day 113 in the FAS were observed across all treatment groups, including placebo. Greater reductions were observed in the KY1005 groups.

FIG. 5A-C graphically depict EASI 50 (**FIG. 5A**), EASI 75 (**FIG. 5B**) and EASI 90 (**FIG. 5C**) responders over time. Progressive increases in the percentages of patients with at least a 50%, 75% and 90% reduction from baseline in EASI were generally observed across all treatment groups, including placebo. The percentages were greater in the KY1005 groups compared to placebo at all time points (with the exception of EASI 90 at Days 15 and 29, where percentages were zero for both the KY1005 low dose and placebo groups). Black represents KY1005 dose of 200 mg/100mg; grey represents KY1005 dose of 500 mg/250 mg; and white represents placebo.

FIG. 6A graphically depicts vIGA 0 (clear) and 1 (almost clear) responders over time. Progressive increases in the percentages of vIGA 0/1 responders over time were generally observed in the KY1005 treatment groups, but not in the placebo group. By Day 113, the percentage of vIGA 0/1 responders was 44.4% (12/27) and 37.0% (10/27) in the KY1005 low and high dose groups, respectively, compared with 8.3% (2/24) in the placebo group. Grey represents KY1005 dose of 200 mg/100mg; black represents KY1005 dose of 500 mg/250 mg; and white represents placebo.

FIG. 6B graphically depicts the proportion of responders maintaining vIGA 0/1 over the study extension. vIGA, validated Investigator Global Assessment.

FIG. 6C graphically depicts percentage change in EASI over time. *Final dose administered at Week 12. EASI, Eczema Area and Severity Index; SD, standard deviation.

FIG. 7 depicts EASI scores in a table for patients receiving high or low dose KY1005 or placebo during the study and through the safety follow up period. This figure represents all patients who achieved a vIGA0/1 at Week 16 and were assessed for efficacy during the safety follow up period. This figure shows that in those subjects who achieved vIGA0/1 at day 113, there was evidence of long and sustained response up to 5.5 months following last dose (~70% of those receiving KY1005).

FIG. 8 graphically depicts the percentage change from Baseline in SCORAD Index between treatment regimens (MMRM analysis). Progressive reductions in SCORAD Index from Baseline to Days

29, 57, 85 and 113 were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points: LSM percentage change (95% CI) in SCORAD Index at Day 113 was -60.30 (-72.57, -48.04) and -58.96 (-71.04, -46.87) for the KY1005 low and high dose groups, respectively, compared to placebo (-36.79 [-49.94, -23.65]).

FIG. 9 graphically depicts percentage change in affected BSA from Baseline over time using LSM with 95% CI. Progressive reductions in affected BSA from Baseline to Days 29, 57, 85 and 113 were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points: Least square means percentage change (95% CI) in affected BSA at Day 113 was -78.07 (-92.35, -63.79) and -71.97 (-86.10, -57.84) for the KY1005 low and high dose groups, respectively, compared to placebo (-41.58 [-57.35, -25.80]).

FIG. 10 graphically depicts percentage change in PO-SCORAD Index from Baseline over time, illustrated using LSM with 95% CI. Progressive reductions in PO-SCORAD Index from Baseline to Days 15, 29, 57, 64, 85 and 113 were generally observed across all treatment groups, including placebo. Greater reductions were observed in the KY1005 groups compared to placebo at nearly all time points: by Day 113, LSM percentage change (95% CI) in PO-SCORAD Index was -55.16 (-69.11, -41.21) and -43.04 (-56.41, -29.67) in the KY1005 low and high dose groups, respectively, versus -23.96 (-38.36, -9.46) in the placebo group.

FIG. 11 graphically depicts percentage change in DLQI total score from baseline over time, illustrated using LSM with 95% CI. Progressive reductions in DLQI total score from baseline to Days 15, 29, 57, 64, 85 and 113 were generally observed across all treatment groups, including placebo. There were generally no clear differences between the treatment groups in the magnitude of the reductions, although there was a trend for greater reductions in the KY1005 treatment groups compared to placebo at Days 85 and 113: by Day 113, LSM percentage change (95% CI) in DLQI total score was -52.99 (-75.31, -30.67) and -59.15 (-80.32, -37.99) in the KY1005 low and high dose groups, respectively, versus -20.51 (-44.95, 3.93) in the placebo group.

FIG. 12 graphically depicts percentage change in mean weekly NRS for pruritus from baseline over time using LSM with 95% CI. Progressive reductions in weekly mean values for NRS for pruritus from Baseline to Days 15, 29, 57, 85 and 113 were generally observed across all treatment groups, including placebo. There were no clear differences between the treatment groups in the magnitude of the reductions at any time point, and none of the comparisons of percentage change in NRS for pruritus between KY1005 groups and placebo revealed a nominally statistically significant difference.

FIG. 13 graphically depicts serum KY1005 concentration versus time data presented using the geometric mean for the main study. Serum concentration profiles for KY1005 were similar between the KY1005 groups, with higher concentrations recorded for the KY1005 high dose group compared

to the low dose group. With repeated I.V. administration, serum concentrations peaked rapidly and subsequently decreased after each dose.

FIG. 14 graphically depicts serum KY1005 concentration versus time data presented using the geometric mean for the extension study. Serum concentration profiles for patients who entered the study extension were similar between the KY1005 groups, with higher KY1005 concentrations recorded for the KY1005 high dose group compared to the low dose group. Following the fourth infusion on Day 85, serum concentrations steadily decreased up to Day 253.

FIG. 15 graphically depicts the overview of study design of Example 3. The study included 3 groups as follows: Comparator Group 1: single dose of 250 mg KY1005, given by IV infusion over 30 min followed by saline flush over 15 min; Group 2: single dose of 125 mg (1 mL) KY1005, given by SC injection into the abdomen; and Group 3: single dose of 250 mg (2 mL) KY1005, given as sequential 2 × 1 mL SC injections into the abdomen.

FIG. 16A-B graphically depicts mean serum concentration time plots of KY1005 up to 92 days after single intravenous and subcutaneous doses that are linear (**FIG. 16A**) and semi-logarithmic (**FIG. 16B**). Absorption *via* the SC route was slower than seen for the IV administered drug: mean serum concentration peaked at 168 h post dose (Day 8) after both 250 mg KY1005 (25,803 ng/mL) and 125 mg (14,222 ng/mL) SC doses. Mean serum concentration after 250 mg IV and SC doses converged at about 20,000 ng/mL on Day 36. After that point, mean serum–concentration time curves for both regimens were closely similar throughout the rest of the sampling period, both falling to about 7,000 ng/mL at Follow-up (Day 92).

FIG. 17A-B graphically depicts mean serum concentration time plots of KY1005 up to 24 hours after single intravenous and subcutaneous doses that are linear (**FIG. 17A**) and semi-logarithmic (**FIG. 17B**). Absorption via the SC route was slower than seen for the IV administered drug. Single 250 mg KY1005 IV doses rapidly achieved peak serum concentrations at the end of infusion (30 min): mean serum concentration was 88,931 ng/mL; individual subject concentrations at end-infusion ranged from 72,391 to 120,333 ng/mL (with a 1.66-fold ratio between subjects at each extreme).

FIG. 18A-D graphically depicts dose-normalized KY1005 PK profiles for IV treatment in different studies including KY1005 FIH HV CT-01 (**FIG. 18A**), KY1005 CT-02 (**FIG. 18B**), and KY1005 CT-04 (**FIG. 18C**). The three studies are overlayed in different colors in **FIG. 18D** (CT-01 = purple, CT-02 = red, CT-04 = orange). The dose-normalized IV profiles showed a two-phasic behavior in alignment with the assumed two-compartmental distribution model.

FIG. 19 graphically depicts dose-normalized KY1005 PK profiles for SC treatment for study KY1005 CT-04. The dose-normalized SC profiles were consistent among each other. The profiles were densely sampled during the first day and during the first week. The maximum concentration (C_{max})

was reached between 4 and 14 days. The SC profiles after 14 days were much flatter than the IV profiles.

FIG. 20 graphically depicts predicted C_{min} at week 24 for induction scenarios I-III (varying doses) and IV-XII (varying regimens). **FIG. 20A** depicts Induction Scenario I (200 mg once every four weeks (Q4W) SC, 100 mg Q4W SC, 50 mg Q4W SC, and 25 mg Q4W SC). **FIG. 20B** depicts Induction Scenario II (300 mg Q4W SC, 250 mg Q4W SC, 200 mg Q4W SC, and 150 mg Q4W SC). **FIG. 20C** depicts Induction Scenario III (500 mg Q4W SC, 450 mg Q4W SC, 400 mg Q4W SC, and 350 mg Q4W SC). **FIG. 20D** depicts Induction Scenario IV (125 mg once every 2 weeks (Q2W) SC, 125 mg Q4W SC, 125 mg once every six weeks (Q6W) SC, and 125 mg once every 8 weeks (Q8W) SC). **FIG. 20E** depicts Induction Scenario V (150 mg Q2W SC, 150 mg Q4W SC, 150 mg Q6W SC, and 150 mg Q8W SC). **FIG. 20F** depicts Induction Scenario VI (200 mg Q2W SC, 200 mg Q4W SC, 200 mg Q6W SC, and 200 mg Q8W SC).

FIG. 21A-F graphically depicts predicted C_{min} at week 24 for induction scenarios I-III (varying doses) and IV-XII (varying regimens). **FIG. 21A** depicts Induction Scenario VII (250 mg Q2W SC, 250 mg Q4W SC, 250 mg Q6W SC, and 250 mg Q8W SC). **FIG. 21B** depicts Induction Scenario VIII (300 mg Q2W SC, 300 mg Q4W SC, 300 mg Q6W SC, and 300 mg Q8W SC). **FIG. 21C** depicts Induction Scenario IX (350 mg Q2W SC, 350 mg Q4W SC, 350 mg Q6W SC, and 350 mg Q8W SC). **FIG. 21D** depicts Induction Scenario X (400 mg Q2W SC, 400 mg Q4W SC, 400 mg Q6W SC, and 400 mg Q8W SC). **FIG. 21E** depicts Induction Scenario XI (450 mg Q2W SC, 450 mg Q4W SC, 450 mg Q6W SC, and 450 mg Q8W SC). **FIG. 21F** depicts Induction Scenario XII (500 mg Q2W SC, 500 mg Q4W SC, 500 mg Q6W SC, and 500 mg Q8W SC).

FIG. 22A-C graphically depicts predicted C_{min} at the end of the maintenance period. **FIG. 22A** depicts maintenance Q8W after week 52, **FIG. 22B** depicts maintenance Q12W after week 52, and **FIG. 22C** depicts maintenance Q16W after week 52.

FIG. 23A-D graphically depicts simulated KY1005 PK profiles for atopic dermatitis (AD) patients stratified by bodyweight. Simulations for bodyweights of 50, 75, 100, 120, and 150 kg are shown. **FIG. 23A** depicts four doses of 62.5 mg KY1005 administered every 4 weeks (Q4W). **FIG. 23B** depicts four doses of 125 mg KY1005 administered Q4W. **FIG. 23C** depicts four doses of 250 mg KY1005 administered Q4W. **FIG 23D** depicts one dose of 500 mg KY1005 followed by three doses of 250 mg administered Q4W.

FIG. 24A-D graphically depicts predicted C_{min} after 24 weeks of induction period. Different regimens (Q2W (**FIG. 24A**), Q4W (**FIG. 24B**), Q6W (**FIG. 24C**), Q8W (**FIG. 24D**)) were distributed over different panels.

FIG. 25A-C graphically depicts predicted time above C_{min} during the maintenance period. Different regimens (Q8W (**FIG. 25A**), Q12W (**FIG. 25B**), Q16W (**FIG. 25C**)) were distributed over different panels.

FIG. 26 graphically depicts the overview of study design of Example 5. Four different SC KY1005 dosing regimens will be tested versus placebo. From baseline up to Day 169 (Week 24), KY1005 will be administered at the following doses and intervals; 500 mg loading dose (given as 2 x 2 mL S.C. administration) followed 28 days later and thereafter with 250 mg every 4 weeks (Q4W) or the following regimens from Baseline: 250 mg Q4W, or 125 mg Q4W or 62.5 mg Q4W or Placebo Q4W.

FIG. 27 graphically depicts Correlation between EASI and IL-13 serum levels at baseline. The figure depicts significant correlation of IL-13 levels with severity of disease at BL, as measured by EASI and SCORAD (data not shown). *Linear regression and correlation analysis with r coefficients and p-values based on Spearman correlations (n=77).

FIG. 28 graphically depicts circulating IL-13 over time. Significant decrease in IL-13 serum levels in patients treated with amlitelimab (KY1005 or 2D10), but not placebo, at Day 113. Decrease maintained until Day 253 in responders‡ to amlitelimab, but not to placebo. The sustained reduction in IL-13 serum levels in amlitelimab-treated patients is treatment dependent and strongly indicates that amlitelimab effectively targets immune dysregulation in AD †Repeated-measures two-way ANOVA plus Tukey's multiple comparison test on fold changes in IL-13 compared with BL (Day 1) for patients with complete dataset at Day 113 (placebo, n=15; amlitelimab low dose, n=20; and amlitelimab high dose, n=20). ns $p>0.05$; ** $p<0.01$; *** $p<0.001$, ****$p<0.0001$. ‡Decrease maintained in all patients, except for one patient treated with amlitelimab low dose whose IL-13 levels increased at Day 169 compared with BL. AD, atopic dermatitis; BL, baseline; CI, confidence interval; EASI, Eczema Area and Severity Index; IL, interleukin; ns, not significant; SCORAD, SCORing of Atopic Dermatitis.

FIG. 29A-F graphically depict the log_{10}-fold change of biomarkers IL-13 (**FIG. 29A-B**), IL22 (**FIG. 29C-D**), and IL-17A (**FIG. 29E-F**) at Baseline (Day 0), Day 29 and Day 113 in patients administered either KY1005 or placebo (**FIG. 29B**, **FIG. 29D** and **FIG. 29F** further show data for patients administered KY1005 low and KY1005 high doses). Data for IL-13 and IL-22 are from the KY1005 CT02 serum analysis. Data for IL-17A are from the KY1005 CT02 OLINK analysis. ns, not significant; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$. Two-way repeated measures ANOVA; Dunnett's multiple comparisons test. **FIG. 29A-B** illustrate that KY1005 is associated with reduction in Th2-related serum cytokine. **FIG. 29C-F** illustrate that KY1005 is associated with reduction in cytokines typically linked to Th22 & Th17 responses.

FIG. 30 graphically depicts the proportion of patients achieving a score of 0 or 1 on the Validated Investigator Global Assessment – Atopic Dermatitis (vIGA-AD) scale at 16 weeks of treatment in groups administered either a high dose of KY1005, a low dose of KY1005, or placebo once every four weeks. ***$p<0.001$ vs placebo (Cochran-Mantel-Haenszel test), **$p<0.001$, *$p<0.05$ vs placebo.

FIG 31A-B graphically depicts the relative protein levels of two proteins (IL-22 in **FIG. 31A**, and IL-13 in **FIG. 31B**) associated with disease severity. IL-22 and IL-13 protein levels were found to be significantly associated (FDR p-value < 0.05) with EASI scores at baseline (first column). This association was also maintained at day 29 and day 113 for both proteins. The coefficient of determination R^2 and p-values were calculated using linear models. Each dot represents a patient sample, the blue line represents the linear regression line, the 95% confidence interval is shown in grey.

FIG. 32A-C graphically depicts the levels of IL-13 (**FIG. 32A**), IL-22 (**FIG. 32B**), and IL-17A (**FIG. 32C**), which are significantly reduced at Day 113 upon KY1005 treatment (FDR p-value <0.05). X-axis shows time in days (data points are at days 0, 29 and 113). Y-axis shows Log_2 change from baseline level.

FIG. 33A-C graphically depicts that IL-13 serum levels at baseline are correlated with disease severity. IL-13 is significantly positively correlated with disease severity as measured by both EASI (**FIG. 33A**) and SCORAD (**FIG. 33B**) at baseline. IL-13 baseline levels are not significantly different between treatment groups (**FIG. 33C**). Spearman correlation of IL-13 and EASI/SCORAD at baseline (n=78). One-Way ANOVA with Tukey's multiple comparisons test.

FIG. 34 graphically depicts circulating IL-13 in different treatment groups between baseline and D113. IL-13 levels normalized to Baseline. n= Number of patients with full set of samples up to D113. Two-way ANOVA + Tukey's multiple comparisons test. IL-13 is significantly reduced in KY1005-treated patients (KY1005-low & -high) at D113, but not in Placebo patients.

FIG. 35A-B graphically depicts D113 vs baseline changes in IL-13 levels, illustrating that IL-13 levels are correlated with disease improvement. Only patients with full set of samples up to D113 included (n=58). Spearman correlation of fold change of IL-13 and EASI (**FIG. 35A**)/SCORAD(**FIG. 35B**) at D113. Weak correlations between changes in IL-13 and EASI (**FIG. 35A**) & SCORAD (**FIG. 35A**) disease improvement at D113.

FIG. 36 graphically depicts that IL-13 serum level changes are maintained past D113 in vIGA 0/1 responders. 24 D169 samples and 15 evaluable D253 samples were obtained from 24 patients classified as responder at D113 (vIGA 0-1). In patients classified as responders at D113 (vIGA 0-1), IL-13 serum reduction was prolonged up to D169 and D253 for those treated with KY1005.

FIG. 37A-C graphically depicts that IL-22 serum levels at baseline are correlated with disease severity. One-Way ANOVA with Tukey's multiple comparisons test Spearman correlation of IL-22 and EASI/SCORAD at baseline (n=78). IL-22 is significantly correlated with disease severity as measured by both EASI (**FIG. 37A**) and SCORAD (**FIG. 37B**) at baseline. IL-22 baseline levels are not significantly different between treatment groups (**FIG. 37C**).

FIG. 38 graphically depicts circulating IL-22 in different treatment groups between baseline and D113. n= Number of patients with full set of samples up to D113. Two-way ANOVA + Tukey's

multiple comparisons test. Significant change in IL-22 levels relative to baseline in KY1005-treated patients at D113 (and at D29 in KY1005-high-treated patients), but not in Placebo patients.

FIG. 39A-B graphically depicts D113 vs baseline changes in IL-22 levels, illustrating that IL-22 levels are correlated with disease improvement. Only patients with full set of samples up to D113 included (n=58). Spearman correlation of fold change of IL-22 and EASI (**FIG. 39A**)/SCORAD(**FIG. 39B**) at D113. Weak correlations between changes in IL-22 and EASI (**FIG. 39A**) & SCORAD (**FIG. 39A**) disease improvement at D113.

FIG. 40 graphically depicts that IL-22 serum level changes are maintained past D113 in vIGA 0/1 responders. 24 D169 samples and 16 evaluable D253 samples were obtained from 24 patients classified as responder at D113 (vIGA 0-1). In patients classified as responder at D113 (vIGA 0-1), IL-22 serum reduction was prolonged up to D169 and D253 for those treated with KY1005.

FIG. 41 graphically depicts the effect of Amlitelimab on serum biomarkers (total IgE, IL-13, IL-22 and IL-31). Fold change from baseline in serum (A) IgE, (B) IL-13, (C) IL-22 and (D) IL-31 over time by treatment regimen. Up to week 16, all patients with biomarker data at baseline and week 16 or at least two alternative on-treatment timepoints were included. For the study extension, only patients who achieved vIGA0/1 at week 16 (w16 responders) were included. Post-hoc linear mixed-effects model with Dunnett's multiple comparison test for log10-transformed fold change from baseline by treatment regimen (ns not significant, * $p<0.05$, ** p,0.01, *** $p<0.001$, **** $p<0.0001$). Median + 95% confidence interval; sample size displayed above x-axis.

FIG. 42 graphically depicts on-treatment IL-31 serum levels changes in time.

Detailed Description

In a first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection. The antibody or fragment thereof may be administered via subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug. After administering the disease modifying drug, the subject may achieve an IGA-AD score of 0 or 1 for at least six months. Any other suitable disease severity measure

described herein, such as EASI75 or EASI90, which may indicate disease modification, may be substituted for an IGA-AD score of 0 or 1. The at least six months may be at least seven months, at least eight months or at least nine months. After treatment with the disease modifying drug is stopped, the subject may maintain an IGA-AD score of 0 or 1 for at least six months. The at least six months may be at least seven months, at least eight months or at least nine months. A therapeutic effect may persist after the last administration of the antibody or fragment thereof by at least around six half lives of the antibody or fragment thereof. The at least six half lives may be at least around seven half lives, at least around eight half lives or at least around nine half lives of the antibody or fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered via subcutaneous injection. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months.

The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 5.5 months, at least one interval of 2 to 5 months, at least one interval of 2 to 4.5 months, or at least one interval of 2 to 4 months. The antibody or fragment thereof may be administered at least twice with at least one interval of around 3 months. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 5.5 months, at least one interval of 5 months, at least one interval of 4.5 months, or at least one interval of 4 months. The antibody or fragment thereof may be administered at least twice with at least one interval of around 3 months. Any period expressed in months may alternatively be expressed in weeks, for example in one embodiment one month is equal to four weeks. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the subject is a chronic Atopic

Dermatitis patient. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration EASI score is reduced at least 10% relative to a baseline EASI score. The post-administration EASI score may be reduced at least 10% relative to the baseline EASI score on day 15 through at least day 113 (optionally on day 7 through at least day 113 or on day 29 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration EASI score may be reduced at least 10% relative to the baseline EASI score on day 15 through at least day 169 or at least day 253 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration EASI score may be reduced at least 20% relative to the baseline EASI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration EASI score may be reduced at least 15%, at least 20%, at least 30%, at least 40% or at least 45% relative to the baseline EASI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline vIGA-AD score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration vIGA-AD score is reduced at least 10% relative to a baseline vIGA-AD score. The post-administration vIGA-AD score may be reduced at least 10% relative to the baseline vIGA-AD score on day 15 through at least

day 113 (optionally on day 7 through at least day 113 or on day 29 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration vIGA-AD score may be reduced at least 10% relative to the baseline vIGA-AD score on day 15 through at least day 169 or at least day 253 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration vIGA-AD score may be reduced at least 20% relative to the baseline vIGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration vIGA-AD score may be reduced at least 15%, at least 20%, at least 30%, at least 40% or at least 45% relative to the baseline vIGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, IGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration IGA-AD score is reduced at least 10% relative to a baseline IGA-AD score. The post-administration IGA-AD score may be reduced at least 10% relative to the baseline IGA-AD score on day 15 through at least day 113 (optionally on day 7 through at least day 113 or on day 29 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration IGA-AD score may be reduced at least 10% relative to the baseline IGA-AD score on day 15 through at least day 169 or at least day 253 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration IGA-AD score may be reduced at least 20% relative to the baseline IGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration IGA-AD score may be reduced at least 15%, at least 20%, at least 30%, at least 40% or at least 45% relative to the baseline IGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be

administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, BSA score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration BSA score is reduced at least 10% relative to a baseline BSA score. The post-administration BSA score may be reduced at least 10% relative to the baseline BSA score on day 29 through at least day 113 (optionally on day 7 through at least day 113 or on day 15 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration BSA score may be reduced at least 20% relative to the baseline BSA score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration BSA score may be reduced at least 30% or at least 35% relative to the baseline BSA score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, SCORAD index, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, SCORAD index, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration SCORAD index is reduced at least 10% relative to a baseline SCORAD index. The post-administration SCORAD index may be reduced at least 10% relative to the baseline SCORAD index on day 29 through at least day 113 (optionally on day 7 through at least day 113 or on day 15 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration SCORAD index may be reduced at least 20% relative to the baseline SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration SCORAD index may be reduced at least 30% or at least 35% relative to the baseline SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration SCORAD index may be reduced at least 45% or at least 60% relative to the baseline SCORAD index on around day 113 after administration of the anti-

OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, PO-SCORAD index and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, PO-SCORAD index and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration PO-SCORAD index is reduced at least 10% relative to a baseline PO-SCORAD index. The post-administration PO-SCORAD index may be reduced at least 10% relative to the baseline PO-SCORAD index on day 29 through at least day 113 (optionally on day 7 through at least day 113 or on day 15 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration PO-SCORAD index may be reduced at least 15% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration PO-SCORAD index may be reduced at least 20% or at least 30% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration PO-SCORAD index may be reduced at least 40% or at least 50% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, and/or DQLI score may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index, and/or DQLI score.

In an alternative statement of the first configuration, there is provided a method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein a post-administration DQLI score is reduced at least 10% relative to a baseline DQLI score. The post-administration DQLI score

may be reduced at least 10% relative to the baseline DQLI score on day 85 through at least day 113 (optionally on day 7 through at least day 113 or on day 15 through at least day 113 or on day 29 through at least day 113) after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration DQLI score may be reduced at least 20% relative to the baseline DQLI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The post-administration DQLI score may be reduced at least 30% or at least 35% relative to the baseline DQLI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The antibody or fragment thereof may be administered via injection, optionally subcutaneous injection. The antibody or fragment thereof may be a disease modifying drug. Optionally, the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof. The antibody or fragment thereof may be administered at least twice with at least one interval of 2 to 6 months. The antibody or fragment thereof may be administered at least twice with at least one interval of 6 months. The subject may be a chronic Atopic Dermatitis patient. A post-administration EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index and/or PO-SCORAD index may be reduced at least 10% relative to a corresponding baseline EASI score, vIGA-AD score, IGA-AD score, BSA score, SCORAD index and/or PO-SCORAD index.

Any feature described in connection with one statement of the first configuration is explicitly contemplated in combination with the features of any other statement of the first configuration. Any one statement of the first configuration may be read in combination with any other part of the disclosure, unless otherwise apparent from the context. Any optional features described in any part of this disclosure, in connection with any one statement of the first configuration or any alternative statement of the first configuration, may be read in combination with any other part of the disclosure, unless otherwise apparent from the context.

In a further configuration, there is provided a method of treating inflammatory diseases or inflammatory disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided a method of treating immune-mediated diseases or immune-mediated disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided a method of treating inflammatory skin diseases or inflammatory skin disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating inflammatory diseases or inflammatory disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating immune-mediated diseases or immune-mediated disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating inflammatory skin diseases or inflammatory skin disorders in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

In a further configuration, there is provided a method treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks during induction phase and once every 12 weeks during maintenance phase.

In a further configuration, there is provided a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, via subcutaneous injection.

In a further configuration, there is provided a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks during induction phase and once every 12 weeks during maintenance phase, via subcutaneous injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective

amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via subcutaneous injection.

In a further configuration, there is provided an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks during induction phase and once every 12 weeks during maintenance phase, via subcutaneous injection.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Doses and blood serum concentrations

The dose may be from 20 mg to 1000 mg. The dose may be from 20 mg to 600 mg. The dose may be up to 550 mg, up to 500 mg, up to 450 mg, up to 400 mg, up to 350 mg, up to 300 mg, up to 250 mg, up to 200 mg, up to 150 mg, up to 120 mg, up to 100 mg, or up to 50 mg. The dose may be up to 500 mg, up to 250 mg, or up to 150 mg. The dose may be at least 50 mg, at least 100 mg, at least 120 mg, at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg, at least 350 mg, at least 400 mg, at least 450 mg, at least 500 mg or at least 550 mg. The dose may be at least 50 mg, at least 120 mg or at least 150 mg. The dose may be selected from the group consisting of from 25 mg to 500 mg; from 50 mg to 450 mg; from 100 mg to 350 mg; from 120 mg to 300 mg; from 150 mg to 250 mg; and from 200 mg to 250 mg. The dose may be selected from the group consisting of from 60 mg to 500 mg; from 100 mg to 300 mg or from 125 mg to 150 mg.

The dose may be 62.5 mg, 125 mg, 150 mg, 250 mg or 500 mg. The dose may be 125 mg or 150 mg. The dose may be 125 mg. The dose may be 150 mg. The dose may be 62.5 mg. The dose may be 250 mg. The dose may be 500 mg.

The dose may be of up to 0.6 mg/kg, up to 0.7 mg/kg, up to 0.8 mg/kg, up to 0.9 mg/kg, up to 1 mg/kg, up to 1.1 mg/kg, up to 1.2 mg/kg, up to 1.3 mg/kg, up to 1.4 mg/kg, up to 1.5 mg/kg, up to 1.6 mg/kg, up to 1.7 mg/kg, up to 1.8 mg/kg, up to 1.9 mg/kg, up to 2 mg/kg, up to 2.1 mg/kg, up to 2.2 mg/kg, up to 2.3 mg/kg, up to 2.4 mg/kg, up to 2.5 mg/kg, up to 2.6 mg/kg, up to 2.7 mg/kg, up to 2.8 mg/kg, up to 2.9 mg/kg, up to 3 mg/kg, up to 4 mg/kg, up to 5 mg/kg, up to 6 mg/kg, up to 7 mg/kg, up to 8 mg/kg, up to 9 mg/kg, up to 10 mg/kg, up to 11 mg/kg or up to 12 mg/kg. The dose may be of up to 6 mg/kg or up to 3 mg/kg.

The dose may be of at least 0.45 mg/kg, at least 0.5 mg/kg, at least 0.6 mg/kg, at least 0.7 mg/kg, at least 0.8 mg/kg, at least 0.9 mg/kg, at least 1 mg/kg, at least 1.1 mg/kg, at least 1.2

mg/kg, at least 1.3 mg/kg, at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, at least 3 mg/kg, at least 4 mg/kg, at least 5 mg/kg, at least 6 mg/kg, at least 7 mg/kg, at least 8 mg/kg, at least 9 mg/kg, at least 10 mg/kg, at least 11 mg/kg, or at least 12 mg/kg. The dose may be of at least 0.45 mg/kg. The dose may be of at least 0.7 mg/kg or at least 1.4 mg/kg.

The dose may be selected from the group consisting of from 0.1 mg/kg to 12 mg/kg; from 0.4 mg/kg to 11 mg/kg; from 0.7 mg/kg to 10 mg/kg; from 1 mg/kg to 9 mg/kg; from 1.3 mg/kg to 8 mg/kg; from 1.6 mg/kg to 7 mg/kg; from 1.9 mg/kg to 6 mg/kg; from 2.2mg/kg to 5 mg/kg; from 2.5 mg/kg to 4 mg/kg; from 2.6 mg/kg to 3.8 mg/kg; from 2.7 mg/kg to 3.6 mg/kg; from 2.6 mg/kg to 3.4 mg/kg; from 2.7 mg/mg to 3.3 mg/kg; from 2.8 mg/kg to 3.2 mg/kg; and from 2.9 mg/kg to 3.1 mg/kg.

The dose may be selected from the group consisting of from 0.6 mg/kg to 11 mg/kg; from 0.7 mg/kg to 10 mg/kg; from 0.8 mg/kg to 9 mg/kg; from 0.9 mg/kg to 8 mg/kg; from 1 mg/kg to 7 mg/kg; from 1.1 mg/kg to 6 mg/kg; from 1.2 mg/kg to 5 mg/kg; from 1.3 mg/kg to 4 mg/kg; from 1.4 mg/kg to 3 mg/kg; from 1.5 mg/kg to 2.9 mg/kg; from 1.6 mg/kg to 2.8 mg/kg; from 1.7 mg/mg to 2.7 mg/kg; from 1.8 mg/kg to 2.6 mg/kg; from 1.9mg/kg to 2.5 mg/kg; from 2 mg/kg to 2.4 mg/kg; and from 2.1 mg/kg to 2.3 mg/kg.

The dose may be from 0.7 mg/kg to 6 mg/kg. The dose may be from 1.4 mg/kg to 3 mg/kg.

Preclinical data noted that 0.405 µg/mL IC90 is required for inhibition of OX40L – OX40 interactions, that 1.09 µg/mL IC90 concentration is needed for inhibition of soluble OX40L-induced IL-2 release from primary human T cells and that 1.5 ug/mL IC90 concentration is needed to assess IL-2 decrease in the T cell allogeneic mixed lymphocyte reaction assay. Therefore, preclinical data suggests that minimum concentration needed at the site of action (skin) could to range from 0.405 to 1.5 µg/mL. The dose may be any suitable dose to deliver at least around 0.4 to 1.5 µg/mL to the skin.

The method may comprise administering at least two injections of the antibody or fragment thereof. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a second injection (C_{min}) may be at least about 2.5 µg / ml.

The method may comprise administering at least three injections of the antibody or fragment thereof. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a second injection and prior to administration of a third injection (C_{min}) may be at least about 2.5µg/ml. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a third injection (C_{min}) may be at least about 2.5µg/ml.

The method may comprise administering at least four injections of the antibody or fragment thereof. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a third injection and prior to administration of a fourth injection (C_{min}) may be at least about 2.5μg/ml. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a fourth injection (C_{min}) may be at least about 2.5μg/ml. The minimum blood serum concentration reached by the antibody or fragment thereof after administration of a second injection and prior to administration of a fourth injection (C_{min}) may be at least about 2.5μg/ml.

The C_{min} in serum between any two injections may be between 2.5 μg/ml and 600 μg/ml. The C_{min} in serum between any two injections may be between 2.5 μg/ml and 375 μg/ml. The C_{min} in serum between any two injections may be between 4 μg/ml and 600 μg/ml. The C_{min} in serum between any two injections may be at least 2.5 μg/ml, 2.6 μg/ml, at least 2.7 μg/ml, at least 2.8 μg/ml, at least 2.9 μg/ml, at least 3 μg/ml, at least 3.1 μg/ml, at least 3.2 μg/ml, at least 3.3 μg/ml, at least 3.4 μg/ml, at least 3.5 μg/ml, at least 3.6 μg/ml, at least 3.7 μg/ml, at least 3.8 μg/ml, at least 3.9 μg/ml, at least 4 μg/ml, at least 4.1 μg/ml, at least 4.2 μg/ml, at least 4.3 μg/ml, at least 4.4 μg/ml, at least 4.5 μg/ml, at least 4.6 μg/ml, at least 4.7 μg/ml, at least 4.8 μg/ml, at least 4.9 μg/ml, at least 5 μg/ml, at least 5.1 μg/ml, at least 5.2 μg/ml, at least 5.3 μg/ml, at least 5.4 μg/ml, at least 5.5 μg/ml, at least 5.6 μg/ml, at least 5.7 μg/ml, at least 5.8 μg/ml, at least 5.9 μg/ml, at least 6 μg/ml, at least 6.5 μg/ml, at least 7 μg/ml, at least 7.5 μg/ml, at least 8 μg/ml, at least 8.5 μg/ml, at least 9 μg/ml, at least 9.5 μg/ml, at least 10 μg/ml, at least 11 μg/ml, at least 12 μg/ml, at least 13 μg/ml, at least 14 μg/ml, at least 15 μg/ml, at least 16 μg/ml, at least 17 μg/ml, at least 18 μg/ml, at least 19 μg/ml, at least 20 μg/ml, at least 25 μg/ml, at least 30 μg/ml, at least 35 μg/ml, at least 40 μg/ml, at least 50 μg/ml, at least 60 μg/ml, at least 70 μg/ml, at least 80 μg/ml, at least 90 μg/ml, or at least 100 μg/ml. The C_{min} in serum between any two injections may be at least about 4 μg/ml, at least about 5 μg/ml, or at least about 20 μg/ml. The C_{min} in serum between any two injections may be at least about 4 μg/ml. The C_{min} in serum between any two injections may be at least about 5 μg/ml. The C_{min} in serum between any two injections may be at least about 20 μg/ml. The C_{min} in serum between any two injections may be up to 600 μg/ml, up to 500 μg/ml, up to 450 μg/ml, up to 400 μg/ml, up to 350 μg/ml, up to 300 μg/ml, up to 275 μg/ml, up to 250 μg/ml, up to 225 μg/ml, up to 200 μg/ml, up to 175 μg/ml, up to 150 μg/ml, up to 125 μg/ml, up to 100 μg/ml, up to 90 μg/ml, up to 80 μg/ml, up to 70 μg/ml, up to 60 μg/ml, up to 50 μg/ml, up to 45 μg/ml, up to 40 μg/ml, up to 35 μg/ml, up to 30 μg/ml, up to 25 μg/ml, up to 23 μg/ml, up to 20 μg/ml, up to 15 μg/ml, up to 10 μg/ml, up to 9 μg/ml, up to 8 μg/ml, up to 7 μg/ml, up to 6 μg/ml, up to 5 μg/ml, up to 4 μg/ml, up to 3 μg/ml, or up to 2.5 μg/ml. The C_{min} in serum may be up to about 50 μg/ml, up to about 25 μg/ml, up to about 15 μg/ml, or up to about 7 μg/ml. The C_{min} in serum may be up to about 50 μg/ml. The C_{min} in serum may be up to about 25 μg/ml. The C_{min} in serum may be up to about 15 μg/ml. The C_{min} in serum may be up to about 7 μg/ml. The C_{min} in serum between any two injections may be selected from the

group consisting of: at least 3 μg/ml and up to 350 μg/ml; at least 10 μg/ml and up to 300 μg/ml; at least 12.5 μg/ml and up to 250 μg/ml; at least 15 μg/ml and up to 250 μg/ml; at least 18 μg/ml and up to 240 μg/ml; at least 20 μg/ml and up to 220 μg/ml; at least 25 μg/ml and up to 190 μg/ml; at least 30 μg/ml and up to 150 μg/ml; at least 35 μg/ml and up to 125 μg/ml; at least 40 μg/ml and up to 90 μg/ml; and at least 50 μg/ml and up to 65 μg/ml.

The above values for C_{min} are given as measured in blood serum. Serum C_{min} values may be converted into tissue C_{min} values. Shah & Betts (2013) mAbs 5:2, 297-305 calculated for mAbs that the distribution in the skin is around 16% of the systemic concentration. Accordingly, a serum C_{min} value of 2.5 μg/ml would lead to a skin C_{min} value of 0.4 μg/ml and a serum C_{min} value of 375 μg/ml would lead to a skin C_{min} value of 60 μg/ml. Alternative conversions are possible based on other distribution values assumed in the field, which may frequently range from around 10% to 15% of the systemic concentration distributing to the skin. Therefore, as a further example, assuming that distribution in skin is 10% the systemic concentration, a serum concentration level of 4 μg/mL would lead to a skin C_{min} value of 0.4 μg/ml and a serum C_{min} value of 600 μg/ml would lead to a skin C_{min} value of 60 μg/ml.

The maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) may be at least about 1.5 μg / ml, at least about 2 μg / ml, at least about 5 μg / ml, at least about 10 μg / ml, at least about 15 μg / ml, at least about 20 μg / ml, at least about 23 μg / ml, at least about 30 μg / ml, at least about 40 μg / ml, at least about 45 μg / ml, at least about 50 μg / ml, at least about 60 μg / ml, at least about 70 μg / ml, at least about 80 μg / ml, at least about 90 μg / ml, at least about 100 μg / ml, at least about 150 μg / ml, at least about 200 μg / ml, at least about 300 μg / ml or at least about 550 μg / ml. The maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is up to about 550 μg / ml, up to about 400 μg / ml, up to about 300 μg / ml, up to about 200 μg / ml, up to about 150 μg / ml, up to about 100 μg / ml, up to about 90 μg / ml, up to about 80 μg / ml, up to about 70 μg / ml, up to about 60 μg / ml, up to about 50 μg / ml, up to about 45 μg / ml, up to about 40 μg / ml, up to about 35 μg / ml, up to about 30 μg / ml, up to about 25 μg / ml, up to about 23 μg / ml, up to about 20 μg / ml, up to about 15 μg / ml, or up to about 10 μg / ml.

In some embodiments, the injection may be intravenous or subcutaneous. In some embodiments, the injection is subcutaneous, and the dose may be 62.5 mg, 125 mg, 150 mg, 250 mg or 500 mg. In some embodiments, the dose may be 125 mg or 150 mg. In other embodiments, the dose may be 125 mg. In still other embodiments, the dose may be 150 mg. In some embodiments, dose may be 62.5 mg. In some embodiments, the dose may be 250 mg. The dose may be 500 mg.

In some embodiments, the injection is subcutaneous and the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and

prior to administration of a subsequent injection (C_{max}) may be 1.5 µg / ml to 275 µg / ml; 2 µg / ml to 200 µg / ml; 5 µg / ml to 150 µg / ml; 5 µg / ml to 100 µg / ml; 10 µg / ml to 80 µg / ml; 10 µg / ml to 25 µg / ml; 25 µg / ml to 50 µg / ml; or 35 µg / ml to 75 µg / ml. The C_{max} may be 10 µg / ml to 80 µg / ml. The C_{max} may be 10 µg / ml to 25 µg / ml. The C_{max} may be 25 µg / ml to 50 µg / ml The C_{max} may be 35 µg / ml to 75 µg / ml.

In some embodiments, the injection is intravenous and the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) may be 6 µg / ml to 550 µg / ml; 15 µg / ml to 400 µg / ml; 20 µg / ml to 300 µg / ml; 30 µg / ml to 200 µg / ml; 30 µg / ml to 90 µg / ml; 40 µg / ml to 105 µg / ml; 95 µg / ml to 150 µg / ml; or 95 µg / ml to 200 µg / ml. The C_{max} may be 30 µg / ml to 200 µg / ml. The C_{max} may be 30 µg / ml to 90 µg / ml. The C_{max} may be 40 µg / ml to 105 µg / ml. The C_{max} may be 95 µg / ml to 150 µg / ml. The C_{max} may be 95 µg / ml to 200 µg / ml.

The method may maintain the blood serum concentration of the antibody or fragment thereof above any C_{min} value disclosed herein and below any C_{max} value disclosed herein, wherein the C_{min} value is below the C_{max} value. For instance, the method may:

- maintain concentrations blood serum range between about 4 to about 15 µg/mL (tissue concentration of 0.4 to 1.5 µg/mL and above, assuming 10 to 15% tissue/skin penetration),
- maintain concentrations blood serum ranging between about 20 to about 45 µg/mL (tissue concentration of 2 to 6.7 µg/mL and above, assuming 10 to 15% tissue/skin penetration),
- maintain concentrations blood serum range between about 5 to about 23 µg/mL (tissue concentration of 0.5 to 3.5 µg/mL and above, assuming 10 to 15% tissue/skin penetration),
- maintain concentrations blood serum around or below 10 µg/mL.

The method may maintain a therapeutically effective concentration of the antibody or fragment thereof after the last administration. For example, a therapeutically effective concentration may be maintained for at least one month, at least two months or at least three months after the last administration. The therapeutically effective concentration may be at or above any C_{min} value disclosed herein and/or at or below any C_{max} value disclosed herein, wherein the C_{min} value is below the C_{max} value. The method may for instance maintain a serum concentration of about 3 to about 12 µg/mL; about 5 to about 12 µg/mL; or about 3 to about 5 µg/mL, optionally at least three months after the last administration.

The area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be at least around 100,000 ng/ml*day, 500,000 ng/ml*day, at least around 600,000 ng/ml*day, at least around 700,000 ng/ml*day, at least around 800,000 ng/ml*day, at least around 900,000 ng/ml*day, at least around 1,000,000 ng/ml*day, at least around 1,100,000 ng/ml*day, at least around 1,300,000 ng/ml*day, at least around 1,500,000 ng/ml*day, at least around 1,700,000 ng/ml*day, at least around 2,000,000 ng/ml*day, at least around 2,500,000 ng/ml*day, at least around 3,000,000 ng/ml*day, at least around 3,300,000

ng/ml*day or at least around 3,500,000 ng/ml*day, eg at least around 1,000,000 ng/ml*day or at least around 3,000,000 ng/ml*day.

The area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be up to around 4,500,000 ng/ml*day, up to around 4,200,000 ng/ml*day, up to around 4,000,000 ng/ml*day, up to around 3,800,000 ng/ml*day, up to around 3,600,000 ng/ml*day, up to around 3,400,000 ng/ml*day, up to around 3,200,000 ng/ml*day, up to around 3,000,000 ng/ml*day, up to around 2,800,000 ng/ml*day, up to around 2,500,000 ng/ml*day, up to around 2,000,000 ng/ml*day, up to around 1,800,000 ng/ml*day, up to around 1,500,000 ng/ml*day, up to around 1,200,000 ng/ml*day or up to around 1,000,000 ng/ml*day, eg up to around 1,500,000 ng/ml*day or up to around 3,800,000 ng/ml*day.

The area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be from around 100,000 ng/ml*day to around 4,500,000 ng/ml*day or around 1,000,000 ng/ml*day to around 3,800,000 ng/ml*day. The area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be from around 900,000 ng/ml*day to around 1,400,000 ng/ml*day or around 2,900,000 ng/ml*day to around 3,800,000 ng/ml*day.

Induction and maintenance

The method may comprise an induction phase and a maintenance phase.

The induction phase may comprise administering one or more induction phase injections of the antibody or fragment thereof, at an induction dose of between 20 and 500 mg; 20 mg and 300 mg; between 50 mg and 300 mg; between 100 mg and 300 mg; or between 150 mg and 300 mg. The induction dose may be between 200 mg and 300 mg; or between 225 mg and 275 mg. The induction dose may be about 500 mg, 250 mg, about 125 mg or about 62.5 mg. The induction dose may be about 250 mg.

The induction phase may be at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks or at least 24 weeks in duration. The induction phase may comprise administering two or more induction phase injections of the antibody or fragment thereof.

Each induction phase injection may be administered at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks or at least 24 weeks apart. Each induction phase injection may be administered 4 weeks apart.

Each induction phase injection may comprise the same mass of the antibody or fragment thereof as each other induction phase injection. The dose of each induction phase injection may be the same.

Alternatively, one or more induction phase injection may have a different mass of the antibody or fragment thereof as one or more or all of the other induction phase injections. The dose of each

induction phase injection may not be the same. A first induction phase injection may be at a loading dose.

The loading dose may comprise up to three times the mass of the antibody or fragment thereof as each subsequent induction phase injection. The loading dose may comprise greater than 2 times and up to three times the mass of the antibody or fragment thereof as each subsequent induction phase injection. The loading dose may comprise up to twice the mass of the antibody or fragment thereof as each subsequent induction dose. The loading dose may comprise up to 1.5 times the mass of the antibody or fragment thereof as each subsequent induction dose.

The loading dose may be between 100 and 600 mg; between 150 and 550 mg; or between 200 and 500 mg. The loading dose may be about 500 mg, about 250 mg or about 125mg. The loading dose may be about 500 mg.

The induction phase may comprise administering two or more induction phase injections of the antibody or fragment thereof. The second induction phase injection may be administered 2 to 16 weeks after a first induction phase injection; administered 3 to 14 weeks after a first induction phase injection; or administered 4 to 12 weeks after a first induction phase injection. A second induction phase injection may be administered 2 to 14 weeks after a first induction phase injection; administered 2 to 12 weeks after a first induction phase injection; administered 2 to 10 weeks after a first induction phase injection; administered 2 to 8 weeks after a first induction phase injection; administered 2 to 7 weeks after a first induction phase injection; or administered 2 to 6 weeks after a first induction phase injection. A second induction phase injection may be administered 3 to 13 weeks after a first induction phase injection; administered 5 to 11 weeks after a first induction phase injection; or administered 6 to 10 weeks after a first induction phase injection; or administered 7 to 9 weeks after a first induction phase injection. A second induction phase injection may be administered 4 to 8 weeks after a first induction phase injection. A second induction phase injection may be administered about 4 weeks or about 8 weeks after a first induction phase injection. A second induction phase injection may be administered 4 weeks after a first induction phase injection.

The induction phase may comprise administering three or more induction phase injections of the antibody or fragment thereof. The third induction phase injection may be administered 2 to 16 weeks after the second induction phase injection; administered 3 to 14 weeks after the second induction phase injection; or administered 4 to 12 weeks after the second induction phase injection. The third induction phase injection may be administered 2 to 14 weeks after the second induction phase injection; administered 2 to 12 weeks after the second induction phase injection; administered 2 to 10 weeks after the second induction phase injection; administered 2 to 8 weeks after the second induction phase injection; administered 2 to 7 weeks after the second induction phase injection; or administered 2 to 6 weeks after the second induction phase injection. The third induction phase injection may be administered 3 to 13 weeks after the second induction phase injection; administered 5 to 11 weeks after the second induction phase injection; or administered 6 to 10 weeks after the

second induction phase injection; or administered 7 to 9 weeks after the second induction phase injection. The third induction phase injection may be administered 4 to 8 weeks after the second induction dose. The third induction phase injection may be administered about 4 weeks or about 8 weeks after the second induction phase injection. The third induction phase injection may be administered 4 weeks after the second induction phase injection. The interval between the first induction phase injection and the second induction phase injection may have the same duration as the interval between the second induction phase injection and the third induction phase injection.

Each induction phase injection may comprise the same mass of the antibody or fragment thereof as each other induction phase injection and/or each interval between induction phase injections may have the same duration as each other interval between induction phase injections. Each induction phase injection may therefore have the same dose. For example, a dose of 250 mg may be administered with every injection of the induction phase. The entire induction phase may have a dosing interval of for example 4 weeks. The induction phase may therefore involve giving a 250 mg dose every four weeks. Alternatively, the induction phase may involve giving a 125 mg dose every four weeks. Alternatively, the induction phase may involve giving a 62.5 mg dose every four weeks. A fixed dosing interval may be used without a fixed dose for every induction phase injection, for example because a loading dose may be administered. The induction phase may therefore involve giving a 500 mg loading dose, followed four weeks later by a 250 mg dose, with further 250 mg doses given every four weeks through the induction phase. Any and all combinations of doses and dose intervals and injection types (e.g., subcutaneous) described herein are explicitly contemplated.

The maintenance phase may comprise administering one or more maintenance phase injections of the antibody or fragment thereof, at a maintenance dose between 20 mg and 300 mg; between 50 mg and 300 mg; between 100 mg and 300 mg; or between 150 mg and 300 mg. The maintenance dose may be between 200 mg and 300 mg; or between 225 mg and 275 mg. The maintenance dose may be about 500 mg, 250 mg, about 125 mg or about 62.5 mg. The maintenance dose may be about 250 mg.

The maintenance phase may be at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks, at least 24 weeks, at least 32 weeks, at least 40 weeks, at least 52 weeks, or at least 100 weeks in duration. The duration of the maintenance phase may be of any suitable length to achieve a clinical objective and may therefore involve any suitable number of maintenance phase injections. The duration of the maintenance phase may therefore be determined by a clinician. The maintenance period may last as long as, in the patient and clinician's opinion, the patient benefits from such maintenance treatment or doesn't experience an adverse event that requires the treatment to be discontinued. For some subjects, the maintenance phase may be indefinite.

The maintenance phase may comprise administering two or more maintenance phase injections of the antibody or fragment thereof. Each maintenance phase injection may be

administered at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks, at least 24 weeks, at least 32 weeks, at least 40 weeks or at least 52 weeks apart.

Each maintenance phase injection may comprise the same mass of the antibody or fragment thereof as each other maintenance phase injection. The dose of the antibody or fragment thereof used in the induction phase may be maintained for the maintenance phase, i.e. the induction phase dose (other than any loading dose) may be the same as the maintenance phase dose. The dosing interval for the maintenance phase may however be longer than the dosing interval for the induction phase. This may be because once a therapeutic effect has been initiated, the maintenance of the therapeutic effect may be possible at a lower tissue concentration of the antibody or fragment thereof. While a similar end may be obtained by maintaining the induction phase dosing interval while reducing the induction phase dose in the maintenance phase, it may be clinically preferable to reduce the number of injections rather than the dose per injection during the maintenance phase.

A second maintenance phase injection may be administered 2 to 16 weeks after a first maintenance phase injection; administered 3 to 14 weeks after a first maintenance phase injection; or administered 4 to 12 weeks after a first maintenance phase injection. A second maintenance phase injection may be administered 2 to 14 weeks after a first maintenance phase injection; administered 2 to 12 weeks after a first maintenance phase injection; administered 2 to 10 weeks after a first maintenance phase injection; administered 2 to 8 weeks after a first maintenance phase injection; administered 2 to 7 weeks after a first maintenance phase injection; or administered 2 to 6 weeks after a first maintenance phase injection. A second maintenance phase injection may be administered 3 to 13 weeks after a first maintenance phase injection; administered 5 to 11 weeks after a first maintenance phase injection; or administered 6 to 10 weeks after a first maintenance phase injection; or administered 7 to 9 weeks after a first maintenance phase injection. A second maintenance phase injection may be administered 4 to 8 weeks after a first maintenance phase injection. A second maintenance phase injection may be administered about 4 weeks or about 8 weeks after a first maintenance phase injection.

The maintenance phase may comprise administering three or more maintenance phase injections of the antibody or fragment thereof. A third maintenance phase injection may be administered 2 to 16 weeks after the second maintenance phase injection; administered 3 to 14 weeks after the second maintenance phase injection; or administered 4 to 12 weeks after the second maintenance phase injection. A third maintenance phase injection may be administered 2 to 14 weeks after the second maintenance phase injection; administered 2 to 12 weeks after the second maintenance phase injection; administered 2 to 10 weeks after the second maintenance phase injection; administered 2 to 8 weeks after the second maintenance phase injection; administered 2 to 7 weeks after the second maintenance phase injection; or administered 2 to 6 weeks after the second maintenance phase injection. A third maintenance phase injection may be administered 3 to 13 weeks after the second maintenance phase injection; administered 5 to 11 weeks after the second

maintenance phase injection; or administered 6 to 10 weeks after the second maintenance phase injection; or administered 7 to 9 weeks after the second maintenance phase injection. A third maintenance phase injection may be administered 4 to 8 weeks after the second maintenance phase injection. A third maintenance phase injection may be administered about 4 weeks or about 8 weeks after the second maintenance phase injection.

The interval between the first maintenance phase injection and the second maintenance phase injection may have the same duration as the interval between the second maintenance phase injection and the third maintenance phase injection.

Each maintenance phase injection may comprise the same mass of the antibody or fragment thereof as each other maintenance phase injection and/or each interval between maintenance phase injections may have the same duration as each other interval between maintenance phase injections. Each maintenance phase injection may therefore have the same dose. For example, a dose of 250 mg may be administered with every injection of the maintenance phase. The entire maintenance phase may have a dosing interval of for example 16 weeks. The maintenance phase may therefore involve giving a 250 mg dose every 16 weeks. Alternatively, the induction phase may involve giving a 125 mg dose every 16 weeks. Alternatively, the induction phase may involve giving a 62.5 mg dose every 16 weeks. For a further example, a dose of 250 mg may be administered with every injection of the maintenance phase. The entire maintenance phase may have a dosing interval of for example 1 weeks. The maintenance phase may therefore involve giving a 250 mg dose every 12 weeks. Alternatively, the induction phase may involve giving a 125 mg dose every 12 weeks. Alternatively, the induction phase may involve giving a 62.5 mg dose every 12 weeks. Any and all combinations of doses and dose intervals and injection types (e.g., subcutaneous) described herein are explicitly contemplated.

The interval between two or more maintenance phase injections may have an equal duration than or a longer duration than the interval between two or more induction phase injections. As described above, the dosing interval for the maintenance phase may however be longer than the dosing interval for the induction phase. Where a constant dosing interval is used for the induction phase and a consistent dosing interval is used for the maintenance phase then this may be a straightforward comparison of intervals, for example when the induction phase dosing interval is four weeks (Q4W) and the maintenance phase dosing interval is four weeks (Q4W) the interval between induction phase injections has an equal duration to the interval between maintenance phase injections. When the induction phase dosing interval is four weeks (Q4W) and the maintenance phase dosing interval is 12 weeks (Q12W) the interval between maintenance phase injections is longer than the interval between maintenance phase injections. The comparison between the dosing interval for the maintenance phase and the dosing interval for the induction phase may alternatively be calculated as the average (mean, median or mode) of all intervals within the induction and maintenance phase respectively. Alternatively, the comparison between the dosing interval for the maintenance phase

and the dosing interval for the induction phase may be calculated by comparing specific examples of dosing intervals as further described below.

The interval between the first maintenance phase injection and the second maintenance phase injection may have an equal duration than or a longer duration than the interval between two or more induction phase injections. The interval between two or more induction phase injections may be about 2 weeks, about 4 weeks or about 8 weeks and the interval between two or more maintenance phase injections may be about 12 weeks or about 16 weeks. The interval between two or more induction phase injections may be about 4 weeks or about 8 weeks and the interval between two or more maintenance phase injections may be about 12 weeks. The interval between two or more induction phase injections may be about 4 weeks or about 8 weeks and the interval between two or more maintenance phase injections may be about 16 weeks. The interval between two or more induction phase injections may be about 4 weeks and the interval between two or more maintenance phase injections may be about 16 weeks. The interval between two or more induction phase injections may be about 4 weeks and the interval between two or more maintenance phase injections may be about 12 weeks. The interval between two or more induction phase injections may be about 4 weeks and the interval between two or more maintenance phase injections may be about 4 weeks. The interval between two or more induction phase injections may be about 8 weeks and the interval between two or more maintenance phase injections may be about 8 weeks. The interval between two or more induction phase injections may be about 2 weeks and the interval between two or more maintenance phase injections may be about 8 weeks.

The interval between three or more induction phase injections may be constant. Alternatively, the interval between three or more maintenance phase injections may vary.

The combined duration of the induction phase and the maintenance phase may be at least 52 weeks. The combined duration of the induction phase and the maintenance phase may be any duration achieved by totaling any duration of the induction phase described herein with any duration of the maintenance phase described herein. The combined duration of the induction phase and the maintenance phase may be indefinite, since the maintenance phase may be indefinite.

The subject may be transitioned from the induction phase to the maintenance phase based on:

(a) clinical response; and/or

(b) the time since the administration of the first induction phase injection.

The clinical response may be defined by any post-administration score or index described herein. The clinical response may be achieving EASI50, EASI75, EASI90 or EASI100. The clinical response may be achieving IGA-AD0/1 and/or a reduction of at least 2 IGA-AD points. The clinical response is achieving a reduction of at least 3 NRS points or at least 4 NRS points. The clinical response may be determined at any clinically suitable time point, such as 16 weeks, 20 weeks or 24 weeks after the administration of the first induction phase injection.

The transition from the induction phase to the maintenance phase may take place 16 or more weeks after the administration of the first induction phase injection. The transition from the induction phase to the maintenance phase may take place 24 or more weeks after the administration of the first induction phase injection. The transition from the induction phase to the maintenance phase may take place up to one year after the administration of the first induction phase injection. The transition from the induction phase to the maintenance phase may take place 16 to 24 weeks after the administration of the first induction phase injection.

In some instances, the transition from the induction phase to the maintenance phase may take place based on a clinical response determined during the induction phase. This may occur for example when some time is needed to analyse data on disease severity. There may therefore be a lag between gathering the data on which a clinical response can be determined and transitioning the subject from the induction phase to the maintenance phase. The clinical response may for example be assessed at week 16 by collecting data on disease severity leading to a later transition from the induction phase to the maintenance phase if the clinical response is positive, for example at week 24 after the administration of the first induction phase injection. The decision to transition from the induction phase to the maintenance phase may further account for additional information available since the data on which a clinical response was determined were gathered, for example a subsequent clinical assessment at the time of transitioning from the induction phase to the maintenance phase.

The transition from the induction phase to the maintenance phase may take place at 24 weeks if the subject has achieved a clinical response of at least EASI75 at 16 weeks.

The induction phase may be a variable induction phase. By "variable" is meant the duration of the induction phase will vary between subjects and transition from induction phase to maintenance phase will depend on patient specific factors. The patient specific factors may include clinical response. For example the transition may occur when a patient has achieved IGA0/1, has clear/almost clear skin, has achieved EASI 50, has achieved EASI75 or has achieved EASI90.

The administration may be subcutaneous. The subcutaneous injection may be to any suitable side of injection, such as the abdomen or the outside of the thigh. In some embodiments, subcutaneous administration is used for treatment of Atopic Dermatitis because this is more convenient for patients and less resource intensive than intravenous injection. Any of the methods described herein may involve subcutaneous administration. The methods involves an induction and a maintenance period are primarily intended for use when administration is subcutaneous.

The method may comprise any one of the following four configurations of the induction and/or maintenance phase, administration for each of which may be subcutaneous:

1. The induction phase may comprise administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and

wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

2. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

3. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 125 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

4. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 62.5 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

As used in the configurations set out herein "at least 4 weeks" may for instance be 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks or 24 weeks. As

used in the four configurations above "at least 4 weeks" may for instance be 4 weeks, 12 weeks or 16 weeks. This applies to the periods between induction phase injections, between final induction phase injection and first maintenance phase injection and between maintenance phase injections.

The method may comprise administering at least six induction phase injections or at least seven induction phase injections. The first maintenance phase injection may be administered from 4 weeks to 24 weeks or 4 weeks to 16 weeks after the final induction phase injection. The first maintenance phase injection may be administered 12 weeks after the final induction phase injection. The first maintenance phase injection may be administered 16 weeks after the final induction phase injection. The first maintenance phase injection may be administered 24 weeks after the final induction phase injection. The second maintenance phase injection and each subsequent maintenance phase injection may be administered from 4 weeks to 24 weeks or 4 weeks to 16 weeks after the preceding maintenance phase injection. The second maintenance phase injection and each subsequent maintenance phase injection may be administered 12 weeks after the preceding maintenance phase injection. The second maintenance phase injection and each subsequent maintenance phase injection may be administered 16 weeks after the preceding maintenance phase injection. The second maintenance phase injection may be administered 24 weeks after the preceding maintenance phase injection.

The method may:

(a) comprise administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered at least 12 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

The method may comprise any one of the following four further configurations of the induction and/or maintenance phase, administration for each of which may be subcutaneous:

1'. The induction phase may comprise administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection.

2'. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection.

3'. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 125 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection.

4'. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 62.5 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection.

The method may comprise any one of the following four further configurations of the induction and/or maintenance phase, administration for each of which may be subcutaneous:

1". The induction phase may comprise administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after

the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection, wherein the subject has achieved a clinical response of at least EASI75 at 16 weeks after the first induction phase injection.

2". The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection, wherein the subject has achieved a clinical response of at least EASI75 at 16 weeks after the first induction phase injection.

3". The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 125 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection, wherein the subject has achieved a clinical response of at least EASI75 at 16 weeks after the first induction phase injection.

4". The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 62.5 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 16 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 16 weeks after the preceding maintenance phase injection, wherein the subject has achieved a clinical response of at least EASI75 at 16 weeks after the first induction phase injection.

The method may comprise any one of the following four further configurations of the induction and/or maintenance phase, administration for each of which may be subcutaneous:

1‴. The induction phase may comprise administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

2‴. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

3'''. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

4'''. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

The method may comprise any one of the following four further configurations of the induction and/or maintenance phase, administration for each of which may be subcutaneous:

1''''. The induction phase may comprise administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection.

2‴. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection.

3‴. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection.

4‴. The induction phase may comprise administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection. The maintenance phase may comprise:

(a) wherein the subject has achieved a clinical response of at least EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection, or

(ii) the subject is withdrawn from the antibody or fragment thereof;

(b) wherein the subject has not achieved a clinical response of EASI75 and/or IGA-AD 0/1 at 16 weeks after the first induction phase injection:

(i) administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 12 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent

maintenance phase injection is administered at least 12 weeks after the preceding maintenance phase injection.

The method may:

(a) comprise administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 4 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 4 weeks after the preceding maintenance phase injection.

The method may:

(a) comprise administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 12 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 12 weeks after the preceding maintenance phase injection.

The method may:

(a) comprise administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 16 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 16 weeks after the preceding maintenance phase injection.

The method may:

(a) comprise administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 24 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 24 weeks after the preceding maintenance phase injection.

According to one embodiment, the method is a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks or once every 12 weeks or once every 6 months.

According to another embodiment, the method is a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or

fragment thereof is administered once every 4 weeks or once every 12 weeks or once every 6 months via subcutaneous injection.

According to another embodiment, the method is a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks or once every 12 weeks or once every 6 months.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Loading and treatment doses

The method may comprise:

(a) administering a first injection as a loading dose of the antibody or fragment thereof, followed by

(b) administering at least a second injection as a first treatment dose of the antibody or fragment thereof.

The second injection may be administered 3 to 5 weeks after the first injection.

The method may further comprise administering at least a third injection as a treatment dose of the antibody or fragment thereof. The third injection may be administered 3 to 5 weeks after the second injection.

The method may further comprise administering at least a fourth injection as a treatment dose of the antibody or fragment thereof. The fourth injection may be administered 3 to 5 weeks after the third injection.

The method may comprise administering a fifth injection as a treatment dose. The fifth injection may be administered 3 to 5 weeks after the fourth injection.

The method may further comprise administering a sixth injection as a treatment dose. The sixth treatment dose may be administered 3 to 5 weeks after the fifth injection.

Each injection as a treatment dose may be administered 4 weeks after the preceding treatment dose.

The number of injections as treatment doses may be of any suitable number to achieve a clinical objective and may therefore involve any suitable number of injections as treatment doses. The number of injections as treatment doses may therefore be determined by a clinician. For example, the number of treatment does may be at least 6, at least 7, at least 8, at least 9 or at least 10. For some subjects, an indefinite number of injections as treatment doses may be administered.

The loading dose may comprise up to three times the mass of the antibody or fragment thereof as each subsequent injection as a treatment dose. The loading dose may comprise greater than 2 times and up to three times the mass of the antibody or fragment thereof as each subsequent injection as a treatment dose. The loading dose may comprise up to twice the mass of the antibody or fragment thereof as each subsequent injection as a treatment dose. The loading dose may comprise up to 1.5 times the mass of the antibody or fragment thereof as each subsequent injection as a treatment dose.

Each treatment dose may comprise the same mass of the antibody or fragment thereof as each other treatment dose.

The loading dose may be between 100 and 600 mg; between 150 and 550 mg; or between 200 and 500 mg. The loading dose may be 200mg or 500 mg.

Each treatment dose may be between 50 and 300 mg; or between 100 and 250 mg. Each treatment dose may be 100 mg or 250 mg.

An advantage of some embodiments is derived from the good safety profile of the antibody or fragment thereof. This allows a wide range of treatment doses to be used with a loading dose, which may not be advisable for other antibodies where higher doses could, for example, lead to toxicity or unacceptable side-effects. Any dose described herein may be used as a loading dose. Any dose described herein may be used as a treatment dose. Any dose described herein may be used as a treatment dose, with double the treatment dose being used as a loading dose. For example: a loading dose of 500 mg may be combined with a treatment dose of 250 mg; a loading dose of 250 mg may be combined with a treatment dose of 125 mg; or a loading dose of 125 mg may be combined with a treatment dose of 62.5 mg. KY1005 has a particularly advantageous safety profile and may be used with a loading dose when the treatment dose is any dose described herein.

A first maintenance injection as a maintenance dose may be administered between 4 and 8 months after the last injection as a treatment dose. One or more further maintenance injections as a maintenance dose is administered at intervals of between 4 and 8 months.

The administration may be intravenous. The injection may be a subcutaneous injection for embodiments comprising a loading dose and a treatment dose in particular. Disclosed herein are data from a randomized, double-blind, placebo-controlled Phase 2a clinical trial in moderate to severe AD, wherein administration was by intravenous injection.

Pharmacokinetic properties

In some embodiments, the antibody or fragment thereof administered have been found to exhibit surprisingly consistent pharmacokinetic (PK) parameter estimates in IV and subcutaneous population PK models. One advantage observed is a linear PK (with the exception of some non-linearity seen in low doses, such as around 0.45 mg/kg, in healthy subjects), allowing the PK model to be described as a "linear two compartment distribution model", for both IV and subcutaneous

administration. Here, the term "linear" refers to the clearance – encompassing the rate of clearance (CL) and the rate of clearance from the central compartment to the second compartment (Q1) – both of which are shown to be linear in the data disclosed herein. The same finding applies in both AD and healthy patients. Without being bound by theory, this may be related to a low expression of OX40L, such that the rate of clearance doesn't change based on concentration of drug (or therefore time).

In some embodiments, the antibody or fragment thereof administered have been found to exhibit surprisingly low immunogenicity. One component of a harmful immune response to a therapeutic protein is the formation of anti-drug antibodies (ADA). The consequences of an immune reaction to a therapeutic protein range from transient appearance of ADAs without any clinical significance to severe life-threatening conditions. Potential clinical consequences of an unwanted immune response include loss of efficacy of the therapeutic protein and serious acute immune effects such as anaphylaxis. ADAs can affect efficacy of a therapeutic protein either by interfering with the pharmacodynamic interaction between the therapeutic protein and its target or by altering its pharmacokinetic profile.

As described in the European Medicines Agency (EMA) Guideline on Immunogenicity assessment of therapeutic proteins (18 May 2017, EMEA/CHMP/BMWP/42832/2005 Rev1, Committee for Medicinal Products for Human Use (CHMP)), products given intravenously may be less immunogenic than drugs given subcutaneously. It is therefore surprising that the population PK profile for treatments of some embodiments are so similar between IV and subcutaneous administration scenarios (based on a single subcutaneous dose). No meaningful effect of ADA is apparent from the data disclosed herein.

Important factors influencing the immunogenicity of therapeutic proteins in general include the origin (e.g., foreign or human) and nature of the active substance (endogenous proteins, post-translational modifications), significant modifications of the therapeutic protein (e.g., pegylation and fusion proteins), product-related (e.g., degradation products, impurities, aggregates) and process-related impurities (host cell proteins, lipids or DNA, microbial contaminants), formulation (excipients) and the interactions between the drug and/or formulation with the primary product packaging (e.g., containers, closures).

Without being bound by theory, the antibody or fragment thereof administered according to some embodiments may advantageously maintain the native conformation of the antibody or fragment thereof. Denaturation and aggregation of a therapeutic protein may potentially trigger an immune response. Aggregation and adduct formation of proteins may reveal new epitopes or lead to the formation of multivalent epitopes, which may stimulate the immune system. In addition, aggregation can enhance a protein-specific immune response and lead to the formation of ADAs. Higher-molecular weight (MW) aggregates are more prone to elicit immune responses than lower-MW aggregates. The antibody or fragment thereof may exhibit advantageously low aggregation and adduct formation, especially of higher MW aggregates as administered according to some embodiments.

Additional factors influencing the immunogenicity of therapeutic proteins include properties of the active ingredient. Therapeutic protein analogues to human endogenous proteins may trigger an immune response due to variations in the amino acid sequence or changes to the protein structure compared to the endogenous protein as a result of post-translational modifications, or other changes during all steps of the drug substance and/or drug product manufacturing process, storage and administration. T cell epitopes are small linear peptides and may thus be modified by a difference in the amino acid sequence between an endogenous and a therapeutic protein. Accordingly, analyses to identify potential T cell epitopes may be helpful for selection of novel proteins or peptides for development. Glycosylation can influence both the physico-chemical and biological properties of a protein. The presence or absence, as well as the structure of carbohydrate moieties may have both a direct or indirect impact on the immunogenicity of therapeutic proteins; the glycan can induce an immune response itself (e.g., glycans of non-human origin), or its presence may affect the conformation of the protein in such a way that the protein becomes immunogenic. In some embodiments, the antibody or fragment thereof administered may advantageously minimise such properties and therefore minimise immunogenicity.

The antibody or fragment thereof may be capable of exhibiting one or more pharmacokinetic properties selected from the group consisting of:

(a) a rate of clearance (CL) of about 0.05 to about 0.18 L/day;

(b) an absorption constant (ka) of about 0.11 to about 0.33 L/day;

(c) a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L;

(d) a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L;

(e) a rate of clearance from the central compartment to the second compartment (Q) of about 0.31 to about 0.93 L/day; and

(f) a bioavailability (Fabs1) of about 0.6 to about 1.0.

The antibody or fragment thereof may have 1, 2, 3, 4, 5, or 6 of the pharmacokinetic properties (a) to (f).

The antibody or fragment thereof may exhibit a rate of clearance (CL) of about 0.05 to about 0.18 L/day; about 0.06 to about 0.17 L/day; about 0.07 to about 0.16 L/day; about 0.08 to about 0.15 L/day; about 0.09 to about 0.14 L/day; or about 0.10 to about 0.13 L/day. The antibody or fragment thereof may exhibit a rate of clearance (CL) of about 0.115 L/day.

The antibody or fragment thereof may exhibit an absorption constant (ka) of about 0.11 to about 0.33 L/day; about 0.12 to about 0.32 L/day; about 0.13 to about 0.31 L/day; about 0.14 to about 0.30 L/day; about 0.15 to about 0.29 L/day; about 0.16 to about 0.28 L/day; about 0.17 to about 0.27 L/day; about 0.18 to about 0.26 L/day; about 0.19 to about 0.25 L/day; about 0.20 to about 0.24 L/day; or about 0.21 to about 0.23 L/day. The antibody or fragment thereof may exhibit an absorption constant (ka) of about 0.22 L/day.

The antibody or fragment thereof may exhibit a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L; about 1.8 to about 4.8 L; about 2.0 to about 4.6 L; about 2.2 to about 4.4 L; about 2.4 to about 4.2 L; about 2.6 to about 4.0 L; about 2.8 to about 3.8 L; about 3.0 to about 3.6 L; or about 3.2 to about 3.4 L. The antibody or fragment thereof may exhibit a volume of central compartment volume (Vc) of about 3.3 L.

The antibody or fragment thereof may exhibit a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L; about 1.4 to about 3.4 L; about 1.6 to about 3.2 L; about 1.8 to about 3.0 L; about 2.0 to about 2.8 L; about 2.2 to about 2.6 L; or about 2.3 to about 2.5 L. The antibody or fragment thereof may exhibit a second (peripheral compartment) volume (Vp1) of about 2.4 L.

The antibody or fragment thereof may exhibit a rate of clearance from the central compartment to the second compartment (Q1) of about 0.31 to about 0.93 L/day; about 0.36 to about 0.88 L/day; about 0.41 to about 0.83 L/day; about 0.46 to about 0.78 L/day; about 0.51 to about 0.73 L/day; about 0.56 to about 0.68 L/day; about 0.60 to about 0.64 L/day; or about 0.61 to about 0.63 L/day. The antibody or fragment thereof may exhibit a rate of clearance from the central compartment to the second compartment (Q1) of about 0.62 L/day.

The antibody or fragment thereof may exhibit a bioavailability (Fabs1) of about 0.6 to about 1.0; about 0.65 to about 0.95; about 0.70 to about 0.90; or about 0.75 to about 0.85. The antibody or fragment thereof may exhibit a bioavailability (Fabs1) of about 0.8.

The pharmacokinetic properties may result from administration of a single dose of the antibody, or fragment thereof. The pharmacokinetic properties may alternatively result from administration of more than one dose (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) of the antibody, or fragment thereof. The subject may be dosed with the antibody or fragment thereof such that the antibody or fragment thereof is present in the subject at a steady state level.

The pharmacokinetic properties may be determined based on samples from a single subject. The pharmacokinetic properties may alternatively be determined based on samples of a population, e.g., a mixed population (e.g., healthy and not healthy), a population with AD, or a population with moderate to severe AD.

Said pharmacokinetic properties may be determined using a two-compartment model. The two-compartment model may be a linear two-compartment model. In a linear two-compartment model, CL and Q1 may be linear with respect to the concentration of the antibody or fragment thereof.

The antibody or fragment thereof may have at least any two of the pharmacokinetic properties above as determined using a two-compartment model. The antibody or fragment thereof may have at least any three of the pharmacokinetic properties above as determined using a two-compartment model. The antibody or fragment thereof may have at least any four of the pharmacokinetic properties above as determined using a two-compartment model. The antibody or fragment thereof may have at least any five of the pharmacokinetic properties above as determined using a two-compartment

model. The antibody or fragment thereof may have six of the pharmacokinetic properties above as determined using a two-compartment model.

The pharmacokinetic properties may result from administration of the antibody of fragment thereof by intravenous injection or by subcutaneous injection. The pharmacokinetic properties may result from administration of any dose or combination of doses described herein.

The method may further comprise obtaining one or more blood samples from the subject and optionally measuring the blood serum concentration reached by the antibody or fragment thereof.

Patient populations

The subject is a human subject. The subject may be a male subject. The subject may be a female subject. The subject may be between about 6 and about 100 years of age; about 15 and about 100 years of age; about 18 and about 93 years of age; about 20 and about 80 years of age; about 30 and about 70 years of age; or about 40 and about 60 years of age. The subject may be about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100 years of age. The subject may be 44 years of age. The subject may weigh about 92 kg. The subject may weigh between about 40 and about 210 kg. The subject may weigh between about 50 and 200 kg, about 60 and about 150 kg; or about 75 and about 100 kg. The subject may weigh about 40, 43, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 92, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205 or 210 kg.

The subject may have an age selected from the group consisting of up to 6 years of age; from 6 years of age to 12 years of age; from 12 years of age to 18 years of age; at least 18 years of age; and less than 75 years of age. The subject may be at least 18 years of age and/or less than 75 years of age. The subject may have an age of 6 months to 11 years. The subject may have an age of 12 years to 17 years.

The subject may be an inflammatory diseases or inflammatory disorders patient. The subject may be an immune-mediated diseases or immune-mediated disorders. The subject may be an inflammatory skin diseases or inflammatory skin disorders patient.

The subject may be a Type 2 patient. The subject may be a high Type 2 patient. The subject may be a low Type 2 patient. The subject may be a non-Type 2 patient. The subject may be a patient with mixed inflammatory responses.

The subject may have been diagnosed with Atopic Dermatitis at least one year before administration of the antibody or fragment thereof. The subject may be a chronic Atopic Dermatitis patient. The antibody or fragment thereof may be a first line treatment. The antibody or fragment thereof may be a second line treatment. The Atopic Dermatitis may be moderate-to-severe Atopic Dermatitis. The

Atopic Dermatitis may be not adequately controlled with topical prescription and/or systemic therapies or when those therapies are not advisable.

The subject may be a moderate-to-severe Atopic Dermatitis patient who is candidate for systemic therapy. The subject may be a moderate-to-severe Atopic Dermatitis patient whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The subject may be defined by biomarker levels. The biomarker levels may be any suitable biomarker levels known in the art or described elsewhere herein.

Topical corticosteroids

Topical corticosteroids are a type of steroid medicine applied directly to the skin to reduce inflammation and irritation. Topical corticosteroids may be used for treatment of AD, for example to reduce swelling, redness and itching during flare-ups. When used correctly, topical corticosteroids serious side effects tend to be rare, although are reported. However, they may not be sufficiently effective as the sole treatment for many subject's AD, especially when the AD is moderate to severe AD. An approach described herein is benefitting from the use of topical corticosteroids by also treating with an anti-OX40L antibody, or antigen-binding fragment thereof, in accordance with embodiments of the method.

The Atopic Dermatitis may be resistant, non-responsive or inadequately responsive to treatment by either topical corticosteroids and/or systemic therapies or when those therapies are not advisable or wherein the subject has had an inadequate response to, was intolerant to, or is refractory to one or more topical corticosteroids. The Atopic Dermatitis may not be adequately controlled or inadequately responsive to treatment by topical corticosteroids. The subject may have had an inadequate response to, was intolerant to, or is refractory to one or more topical corticosteroids. The subject may also be being treated with one or more topical corticosteroids. The antibody or fragment thereof may be used with topical corticosteroids. The subject may have been previously treated with one or more topical corticosteroid.

The method may further comprise administering a therapeutically effective amount of one or more topical corticosteroid. The one or more topical corticosteroid may be administered prior to the anti-OX40L antibody, or antigen-binding fragment thereof. A first injection of the anti-OX40L antibody, or antigen-binding fragment thereof may be administered on the day that the subject discontinues treatment with the one or more topical corticosteroid. A first injection of the anti-OX40L antibody, or antigen-binding fragment thereof may be administered on the day that a clinical decision is taken to discontinue treatment with the one or more topical corticosteroid.

A clinical decision to discontinue treatment with the one or more topical corticosteroid may be taken or the subject may discontinue treatment for a number of reasons. For example, the subject

may have an inadequate response to the one or more topical corticosteroid, be intolerant to the one or more topical corticosteroid or be refractory to the one or more topical corticosteroid. The likely time course for discontinuing treatment may depend on the reason for discontinuing treatment. For example, it may be rapidly evident to a clinician that a patient is intolerant to the one or more topical corticosteroid so that the decision to discontinue treatment can be taken relatively quickly. It may take longer to determine that a patient is refractory to, or has an inadequate response to the one or more topical corticosteroid, so the decision to discontinue treatment for these reasons may be taken less quickly accordingly. The reasons may be a primary efficacy failure, a secondary efficacy failure or intolerance. A primary efficacy failure may be where no response to the start of treatment is seen. In this case, the treatment may be discontinued quickly. A secondary efficacy failure may be when a patient loses responsiveness and doesn't respond to further treatment, which may occur at any time after an initial response has been observed, for example after six months, after one year, after 18 months or after two years. Intolerance can be at any time after start of treatment, for some it may be evident early on, for others it may be after a period of time that adverse events start to show.

A clinical decision may be taken to discontinue treatment or the subject may discontinue treatment with the one or more topical corticosteroid at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first administration of the one or more topical corticosteroid.

The one or more topical corticosteroid may be administered after the anti-OX40L antibody, or antigen-binding fragment thereof. A first administration of the one or more topical corticosteroid may be administered on the day that the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof. A first administration of the one or more topical corticosteroid may be administered on the day that a clinical decision is taken to discontinue treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

A clinical decision may be taken to discontinue treatment or the subject may discontinue treatment with the anti-OX40L antibody, or antigen-binding fragment thereof, at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof.

In many instances, the subject may undergo combined treatment with both a topical corticosteroid and the anti-OX40L antibody, or antigen-binding fragment thereof. However, in some instances, The one or more topical corticosteroid and the anti-OX40L antibody, or antigen-binding fragment thereof may be administered sequentially and a period between administering an administration of the one or more topical corticosteroid and an injection of the anti-OX40L antibody, or antigen-binding fragment thereof is at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 10 weeks, at least 12

weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks, at least 40 weeks, at least 44 weeks, at least 48 weeks or at least 52 weeks.

The one or more topical corticosteroid may be administered concurrently with the anti-OX40L antibody, or antigen-binding fragment thereof. Concurrent administration may include overlapping dosage regimes and/or coadministration.

The topical corticosteroid may be any suitable topical corticosteroid. The topical corticosteroid may be selected from the group consisting of betamethasone dipropionate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, diflorasone diacetate, halobetasol propionate, amcinonide, augmented betamethasone dipropionate, fluocinonide, halcinonide, triamcinolone acetonide, betamethasone valerate, clocortolone pivalate, desoximetasone, fluocinolone acetonide, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone valerate, prednicarbate, alclometasone dipropionate, desonide, hydrocortisone and hydrocortisone acetate. The topical corticosteroid may be selected from the group consisting of betamethasone dipropionate, betamethasone dipropionate;gentamicin sulphate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate and mometasone furoate. The topical corticosteroid may be betamethasone dipropionate, optionally wherein the betamethasone dipropionate is combined with gentamicin sulphate.

The topical corticosteroid may be formulated as a cream, ointment, gel, foam, solution, lotion or gel. The topical corticosteroid may be applied twice daily or once daily. The topical corticosteroid may be applied once weekly or twice weekly.

The duration of topical corticosteroid administration may be of any suitable length to achieve a clinical objective and may therefore involve any suitable number of administrations. The duration of topical corticosteroid administration may therefore be determined by a clinician. For some subjects, topical corticosteroid administration may be indefinite.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Calcineurin inhibitors

Topical calcineurin inhibitors (TCIs) work by altering the immune system and have been developed for treating atopic dermatitis. There are two types available: tacrolimus ointment (Protopic) for moderate to severe atopic dermatitis and pimecrolimus cream (Elidel) for mild to moderate atopic dermatitis. 'Topical' means applied to the skin. 'Calcineurin inhibitor' means that they block Calcineurin that can contribute to the flaring of atopic dermatitis. TCIs are used to treat atopic dermatitis in adults and children over 2 years of age who are not responding adequately to or who cannot tolerate

conventional therapies such as topical steroids. They can be used for both treating and preventing flares. An approach described herein is benefitting from the use of topical calcineurin inhibitor by also treating with an anti-OX40L antibody, or antigen-binding fragment thereof, in accordance with the embodiments of the method.

The Atopic Dermatitis may be resistant, non responsive or inadequately responsive to treatment by either topical calcineurin inhibitor and/or systemic therapies or when those therapies are not advisable or wherein the subject has had an inadequate response to, was intolerant to, or is refractory to one or more topical calcineurin inhibitor. The Atopic Dermatitis may not be adequately controlled or inadequately responsive to treatment by topical calcineurin inhibitor. The subject may have had an inadequate response to, was intolerant to, or is refractory to one or more topical calcineurin inhibitor. The subject may also be being treated with one or more topical calcineurin inhibitor. The antibody or fragment thereof may be used with topical calcineurin inhibitor. The subject may have been previously treated with one or more topical calcineurin inhibitor.

The method may further comprise administering a therapeutically effective amount of one or more topical calcineurin inhibitor. The one or more topical calcineurin inhibitor may be administered prior to the anti-OX40L antibody, or antigen-binding fragment thereof. A first injection of the anti-OX40L antibody, or antigen-binding fragment thereof may be administered on the day that the subject discontinues treatment with the one or more topical calcineurin inhibitor. A first injection of the anti-OX40L antibody, or antigen-binding fragment thereof may be administered on the day that a clinical decision is taken to discontinue treatment with the one or more topical calcineurin inhibitor.

A clinical decision to discontinue treatment with the one or more topical calcineurin inhibitor may be taken or the subject may discontinue treatment for a number of reasons. For example, the subject may have an inadequate response to the one or more topical calcineurin inhibitor, be intolerant to the one or more topical calcineurin inhibitor or be refractory to the one or more topical calcineurin inhibitor. The likely time course for discontinuing treatment may depend on the reason for discontinuing treatment. For example, it may be rapidly evident to a clinician that a patient is intolerant to the one or more topical calcineurin inhibitor so that the decision to discontinue treatment can be taken relatively quickly. It may take longer to determine that a patient is refractory to, or has an inadequate response to the one or more topical calcineurin inhibitor, so the decision to discontinue treatment for these reasons may be taken less quickly accordingly. The reasons may be a primary efficacy failure, a secondary efficacy failure or intolerance. A primary efficacy failure may be where no response to the start of treatment is seen. In this case, the treatment may be discontinued quickly. A secondary efficacy failure may be when a patient loses responsiveness and doesn't respond to further treatment, which may occur at any time after an initial response has been observed, for example after six months, after one year, after 18 months or after two years. Intolerance can be at any time after start of treatment, for some it may be evident early on, for others it may be after a period of time that adverse events start to show.

A clinical decision may be taken to discontinue treatment with the one or more topical calcineurin inhibitor at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first administration of the one or more topical calcineurin inhibitor.

The one or more topical calcineurin inhibitor may be administered after the anti-OX40L antibody, or antigen-binding fragment thereof. A first administration of the one or more topical calcineurin inhibitor may be administered on the day that the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof. A first administration of the one or more topical calcineurin inhibitor may be administered on the day that a clinical decision is taken to discontinue treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

A clinical decision may be taken to discontinue treatment or the subject may discontinue treatment with the anti-OX40L antibody, or antigen-binding fragment thereof, at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof.

In many instances, the subject may undergo combined treatment with both a topical calcineurin inhibitor and the anti-OX40L antibody, or antigen-binding fragment thereof. However, in some instances, the one or more topical calcineurin inhibitor and the anti-OX40L antibody, or antigen-binding fragment thereof may be administered sequentially and a period between administering an administration of the one or more topical calcineurin inhibitor and an injection of the anti-OX40L antibody, or antigen-binding fragment thereof is at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks, at least 40 weeks, at least 44 weeks, at least 48 weeks or at least 52 weeks.

The one or more topical calcineurin inhibitor may be administered concurrently with the anti-OX40L antibody, or antigen-binding fragment thereof. Concurrent administration may include overlapping dosage regimes and/or coadministration.

The topical calcineurin inhibitor may be any suitable topical calcineurin inhibitor. The topical calcineurin inhibitor may be tacrolimus ointment or pimecrolimus cream, e.g., tacrolimus ointment.

The topical calcineurin inhibitor may be formulated as a cream, ointment, gel, foam, solution, lotion or gel. The topical calcineurin inhibitor may be applied twice daily or once daily. The topical calcineurin inhibitor may be applied two to three times weekly.

The duration of topical calcineurin inhibitor administration may be of any suitable length to achieve a clinical objective and may therefore involve any suitable number of administrations. The duration of topical calcineurin inhibitor administration may therefore be determined by a clinician. For some subjects, topical calcineurin inhibitor administration may be indefinite.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Other co-treatments

Any other suitable treatment for Atopic Dermatitis may characterise the subject to be treated and/or be used in combination with the antibody or fragment thereof according to the methods described herein.

The subject may also be being treated with one or more topical antihistamine. The antibody or fragment thereof may be used with one or more topical antihistamine.

The subject may also be being treated with one or more oral steroid. The antibody or fragment thereof may be used with one or more oral steroid.

Disease severity

There are several different methods which can be used to assign the severity of disease when assessing atopic dermatitis patients. Each method of assigning disease severity may therefore inform patient selection for embodiments of the methods. Each method of assigning disease severity may be used to monitor subject treatment for the embodiments of the methods. Each method of assigning disease severity may be used to transition a patient from the induction phase to the maintenance phase. Each method of assigning disease severity may be used to identify a treatment as disease modifying. Each method of assigning disease severity may be performed as described below and/or in the Examples, as applicable. The methods of assigning disease severity include:

EASI (including EASI75 and EASI90)

The EASI is a continuous scale (0 (no disease)-72 (most severe disease)) used to assess the severity and extent of atopic dermatitis. It is described for example in Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012 Jan;67(1):99–106 and Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11–8. Methods for determining an EASI score are known and may be as described below and/or in the Examples, as applicable.

In EASI, four disease characteristics of AD (erythema, infiltration/papulation, excoriations, and lichenification) are assessed for severity by the investigator on a scale of 0 (absent) to 3 (severe). The scores are added up for each of the four body regions (head, arms, trunk, and legs). The assigned percentages of body surface area (BSA) for each section of the body are 10% for head, 20% for arms, 30% for trunk, and 40% for legs, respectively. Each subtotal score is multiplied by the BSA represented

by that region. In addition, an area score of 0 to 6 is assigned for each body region, depending on the percentage of AD-affected skin in that area: 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores are multiplied by the area affected. The resulting EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD.

It has been suggested that the severity of AD based on EASI score should be categorized as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; 50.1 to 72.0 = very severe. EASI50 indicates ≥ 50% improvement from baseline. EASI75 indicates ≥ 75% improvement from baseline. EASI90 indicates ≥ 90% improvement from baseline. EASI100 indicates 100% improvement from baseline.

It is thought that the overall minimal clinically important difference (MCID) is 6.6 points.

Baseline scores - EASI

The atopic dermatitis may have been assessed by determining a baseline EASI score. Determining a baseline EASI score may comprise:

(a) Selecting a body region from the group consisting of head and neck; trunk including the genital area; upper extremities; and lower extremities including the buttocks;

(b) Assessing the extent of atopic dermatitis in the selected body region and assigning a region score based on the extent of atopic dermatitis in the selected body region;

(c) Assessing the severity of each of the following signs in the selected body region:

1. Erythema,
2. Edema and/or papulation,
3. Excoriation, and
4. Licenification,

and assigning a severity score to each sign in the selected body region;

(d) Determining a total score for the selected body region based on the region score and the severity score for each sign in the selected body region;

(e) Repeating steps (b) to (d) for each of the remaining body regions; and

(f) Determining a baseline EASI score based on the total score for each body region.

The baseline EASI score may be any score indicating moderate to severe AD. The baseline EASI score may be at least 12.1, at least 16.1, or at least 21.1. The baseline EASI score may be at least 16.1.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline EASI score is determined.

Some embodiments of the method may further comprise determining the baseline EASI score.

Clinical outcomes – EASI

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining a post-administration EASI score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration EASI score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in EASI score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration EASI score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration EASI score may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration EASI score may be determined at the end of the induction phase.

The post-administration EASI score may be less than or equal to 21.0. The post-administration EASI score may indicate the AD is no longer severe AD. The post-administration EASI score may be less than or equal to 16.0. The post-administration EASI score may be less than or equal to 16.0, less than or equal to 15.0, less than or equal to 14.0, less than or equal to 13.0, less than or equal to 12.0, less than or equal to 11.0, less than or equal to 10.0, less than or equal to 9.0, less than or equal to 8.0, less than or equal to 7.0, less than or equal to 6.0, less than or equal to 5.0, less than or equal to 4.0, less than or equal to 3.0, less than or equal to 2.0, less than or equal to 1.0 or around 0. The post-administration EASI score may indicate the AD is no longer moderate AD. The post-administration EASI score may be less than or equal to 7.0 or less than or equal to 1.0. The post-administration EASI score may indicate the AD is mild AD. The post-administration EASI score may indicate the AD is almost clear. The post-administration EASI score may be reduced at least 10 percent, at least 25 percent or at least 50 percent relative to the baseline EASI score. The post-administration EASI score may be reduced at least 6 points, at least 6.6 points, at least 7 points, at least 8 points, at least 9 points or at least 10 points relative to the baseline EASI score.

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining one or more further post-administration EASI score. The one or more further post-administration EASI score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration EASI score may be determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days

after administering a first injection of the antibody or fragment thereof. The one or more further post-administration EASI score may be determined at the end of the induction phase.

The one or more further post-administration EASI score may be less than or equal to 21.0. The one or more further post-administration EASI score may indicate the AD is no longer severe AD. The one or more further post-administration EASI score may be less than or equal to 16.0, less than or equal to 15.0, less than or equal to 14.0, less than or equal to 13.0, less than or equal to 12.0, less than or equal to 11.0, less than or equal to 10.0, less than or equal to 9.0, less than or equal to 8.0, less than or equal to 7.0, less than or equal to 6.0, less than or equal to 5.0, less than or equal to 4.0, less than or equal to 3.0, less than or equal to 2.0, less than or equal to 1.0 or around 0. The one or more further post-administration EASI score may indicate the AD is no longer moderate AD. The one or more further post-administration EASI score may be less than or equal to 7.0 or less than or equal to 1.0. The one or more further post-administration EASI score may indicate the AD is mild AD. The one or more further post-administration EASI score may indicate the AD is almost clear. The one or more further post-administration EASI score may be reduced at least 10 percent, at least 25 percent or at least 50 percent relative to the baseline EASI score. The one or more further post-administration EASI score is reduced at least 6 points, at least 6.6 points, at least 7 points, at least 8 points, at least 9 points or at least 10 points relative to the baseline EASI score. The one or more further post-administration EASI score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline EASI score. The post-administration EASI score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Determining the post-administration EASI score and/or the one or more further post-administration EASI score may comprise:

(a) Selecting a body region from the group consisting of head and neck; trunk including the genital area; upper extremities; and lower extremities including the buttocks;

(b) Assessing the extent of atopic dermatitis in the selected body region and assigning a region score based on the extent of atopic dermatitis in the selected body region;

(c) Assessing the severity of each of the following signs in the selected body region:

1. Erythema,
2. Edema and/or papulation,
3. Excoriation, and

4. Licenification,

and assigning a severity score to each sign in the selected body region;

(d) Determining a total score for the selected body region based on the region score and the severity score for each sign in the selected body region;

(e) Repeating steps (b) to (d) for each of the remaining body regions; and

(f) Determining a baseline EASI score based on the total score for each body region.

The post-administration EASI and/or further post-administration EASI may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and the post-administration EASI and/or further post-administration EASI may be EASI50, EASI75, EASI90 or EASI100. The post-administration EASI and/or further post-administration EASI may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI may be EASI50, EASI75, EASI90 or EASI100. The post-administration EASI and/or further post-administration EASI may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI may be EASI50, EASI75, EASI90 or EASI100. The Atopic Dermatitis may be treated as evidenced by a reduction in the EASI score by at least 40% after the third injection as a treatment dose and wherein the reduction in EASI score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in EASI score. Some embodiments include therapeutic methods which result in a decrease from baseline in EASI score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration EASI score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline EASI score. The reduction of the post-administration EASI score relative to the baseline EASI score may be derived from any baseline EASI score and any post-administration EASI score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in EASI score of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-

binding fragment thereof to a subject results in a decrease from baseline in EASI score of at least 40% or at least 45%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in EASI score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Investigator Global Assessment – Atopic Dermatitis (IGA-AD)

The IGA-AD scale, which ranges from 0-4, and is assigned by physicians, was developed by Eli Lilly in collaboration with a number of clinical experts in Atopic Dermatitis and was reviewed by the FDA and agreed upon. Methods for determining an IGA-AD score are known and may be as described below and/or in the Examples, as applicable.

A summary of the assignment of the different scores is in Table 1a below.

Score	Morphological Description
0 - Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, and/or barely perceptible induration/papulation. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), and/or slight but definite induration/papulation. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), and/or clearly perceptible induration/papulation. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), and/or marked induration/papulation. Disease is widespread in extent. Oozing or crusting may be present.

Table 1a: IGA-AD scores

A decrease in IGA-AD score therefore relates to an improvement in signs and/or symptoms.

Baseline scores - IGA-AD

The atopic dermatitis may have been assessed by determining a baseline IGA-AD score. Determining a baseline IGA-AD score may comprise describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:

- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:

- Barely perceptible erythema, and/or barely perceptible induration/papulation; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), and/or slight but definite induration/papulation; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), and/or clearly perceptible induration/papulation; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), and/or marked induration/papulation; disease is widespread in extent; oozing or crusting may be present.

The baseline IGA-AD score may be any score indicating moderate to severe AD. The baseline IGA-AD score may be 3 or 4.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline IGA-AD score is determined.

Some embodiments of the method may further comprise determining the baseline IGA-AD score.

Clinical outcomes – IGA-AD

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining a post-administration IGA-AD score at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration IGA-AD score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in IGA-AD score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be

employed. The post-administration IGA-AD score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration IGA-AD score may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration IGA-AD score may be determined at the end of the induction phase.

The post-administration IGA-AD score may be 0 or 1. The post-administration IGA-AD score may indicate the AD is no longer severe AD. The post-administration IGA-AD score may indicate the AD is no longer moderate AD. The post-administration IGA-AD score may indicate the AD is almost clear. The post-administration IGA-AD score may be reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline IGA-AD score. The post-administration IGA-AD score may be reduced at least 2 points relative to the baseline IGA-AD score. The post-administration IGA-AD score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline IGA-AD score. The the post-administration IGA-AD score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining one or more further post-administration IGA-AD score. The one or more further post-administration IGA-AD score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration IGA-AD score is determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration IGA-AD score may be determined at the end of the induction phase.

The one or more further post-administration IGA-AD score may be 0 or 1. The one or more further post-administration IGA-AD score may indicate the AD is no longer severe AD. The one or more further post-administration IGA-AD score may indicate the AD is no longer moderate AD. The one or more further post-administration IGA-AD score may indicate the AD is almost clear. The one or more further post-administration IGA-AD score may be reduced at least 1 point, at least 2 points,

at least 3 points or up to 4 points relative to the baseline IGA-AD score. The one or more further post-administration IGA-AD score may be reduced at least 2 points relative to the baseline IGA-AD score.

Determining the post-administration IGA-AD score and/or the one or more further post-administration IGA-AD score may comprise describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:

- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:

- Barely perceptible erythema, and/or barely perceptible induration/papulation; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), and/or slight but definite induration/papulation; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), and/or clearly perceptible induration/papulation; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), and/or marked induration/papulation; disease is widespread in extent; oozing or crusting may be present.

The post-administration IGA-AD and/or further post-administration IGA-AD may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and the post-administration IGA-AD and/or further post-administration IGA-AD may be:

(a) A IGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline IGA-AD score.

The post-administration IGA-AD and/or further post-administration IGA-AD may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration IGA-AD and/or further post-administration IGA-AD may be:

(a) A IGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline IGA-AD score.

The post-administration IGA-AD and/or further post-administration IGA-AD may be determined at least around 253 days after administering a first injection of the antibody or fragment

thereof and wherein the post-administration IGA-AD and/or further post-administration IGA-AD may be:

(a) A IGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline IGA-AD score.

The Atopic Dermatitis may be treated as evidenced by a reduction in the IGA-AD score by at least 2 points after the third injection as a treatment dose and wherein the reduction in IGA-AD score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments of, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in IGA-AD score. Some embodiments include therapeutic methods which result in a decrease from baseline in IGA-AD score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration IGA-AD score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline IGA-AD score. The reduction of the post-administration IGA-AD score relative to the baseline IGA-AD score may be derived from any baseline IGA-AD score and any post-administration IGA-AD score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in IGA-AD score of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in IGA-AD score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Validated Investigator Global Assessment – Atopic Dermatitis (vIGA-AD)

The vIGA-AD scale, which ranges from 0-4, and is assigned by physicians, was developed by Eli Lilly in collaboration with a number of clinical experts in Atopic Dermatitis and was reviewed by the FDA and agreed upon. Further information can be found in Simpson *et al.*, "The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis", J. Am. Acad. Dermatol., 2020 Sep;83(3):839-846. doi: 10.1016/j.jaad.2020.04.104. Epub 2020 Apr 25. The vIGA-AD scale corresponds to the IGA-AD scale but further takes into account lichenification. Methods for determining a vIGA-AD score are known and may be as described below and/or in the Examples, as applicable.

A summary of the assignment of the different scores is in Table 1b below.

Score	Morphological Description
0 - Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Table 1b: vIGA-AD scores

A decrease in vIGA-AD score therefore relates to an improvement in signs and/or symptoms.

Baseline scores - vIGA-AD

The atopic dermatitis may have been assessed by determining a baseline vIGA-AD score. Determining a baseline vIGA-AD score may comprise describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:

- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:

- Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification; disease is widespread in extent; oozing or crusting may be present.

The baseline vIGA-AD score may be any score indicating moderate to severe AD. The baseline vIGA-AD score may be 3 or 4.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline vIGA-AD score is determined.

Some embodiments of the method may further comprise determining the baseline vIGA-AD score.

Clinical outcomes – vIGA-AD

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining a post-administration vIGA-AD score at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration vIGA-AD score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in vIGA-AD score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration vIGA-AD score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration vIGA-AD score may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the

antibody or fragment thereof. The post-administration vIGA-AD score may be determined at the end of the induction phase.

The post-administration vIGA-AD score may be 0 or 1. The post-administration vIGA-AD score may indicate the AD is no longer severe AD. The post-administration vIGA-AD score may indicate the AD is no longer moderate AD. The post-administration vIGA-AD score may indicate the AD is almost clear. The post-administration vIGA-AD score may be reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline vIGA-AD score. The post-administration vIGA-AD score may be reduced at least 2 points relative to the baseline vIGA-AD score. The post-administration vIGA-AD score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline vIGA-AD score. The post-administration vIGA-AD score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments of the method may further comprise assessing the atopic dermatitis by determining one or more further post-administration vIGA-AD score. The one or more further post-administration vIGA-AD score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration vIGA-AD score is determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration vIGA-AD score may be determined at the end of the induction phase.

The one or more further post-administration vIGA-AD score may be 0 or 1. The one or more further post-administration vIGA-AD score may indicate the AD is no longer severe AD. The one or more further post-administration vIGA-AD score may indicate the AD is no longer moderate AD. The one or more further post-administration vIGA-AD score may indicate the AD is almost clear. The one or more further post-administration vIGA-AD score may be reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline vIGA-AD score. The one or more further post-administration vIGA-AD score may be reduced at least 2 points relative to the baseline vIGA-AD score.

Determining the post-administration vIGA-AD score and/or the one or more further post-administration vIGA-AD score may comprise describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:

- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:

- Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification; disease is widespread in extent; oozing or crusting may be present.

The post-administration vIGA-AD and/or further post-administration vIGA-AD may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and the post-administration vIGA-AD and/or further post-administration vIGA-AD may be:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

The post-administration vIGA-AD and/or further post-administration vIGA-AD may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD may be:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

The post-administration vIGA-AD and/or further post-administration vIGA-AD may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD may be:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

The Atopic Dermatitis may be treated as evidenced by a reduction in the vIGA-AD score by at least 2 points after the third injection as a treatment dose and wherein the reduction in vIGA-AD score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in vIGA-AD score. Some embodiments include

therapeutic methods which result in a decrease from baseline in vIGA-AD score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration vIGA-AD score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline vIGA-AD score. The reduction of the post-administration vIGA-AD score relative to the baseline vIGA-AD score may be derived from any baseline vIGA-AD score and any post-administration vIGA-AD score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in vIGA-AD score of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in vIGA-AD score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin for at least 113 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin for at least 169 days following administration of the anti-OX40L antibody, or antigen-binding fragment

thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin for at least 253 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in an almost clear skin for at least 113 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in an almost clear skin for at least 169 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in an almost clear skin for at least 253 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin for at least 113 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin for at least 169 days following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin for at least 253 days following administration of the anti-OX40L antibody, or antigen-

binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin at least 2 months after administration of the last injection.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin at least 3 months after administration of the last injection.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin at least 4 months after administration of the last injection.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin at least 5 months after administration of the last injection.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a clear skin or an almost clear skin at least 6 months after administration of the last injection.

Numerical Rating Scale (NRS) for pruritus

The Numerical Rating Scale for Pruritus (NRS) is described in Reich *et al*, Acta Derm Venereol 2016 Nov 2;96(7):978-980. As used herein the terms "pruritus" and "itch" are interchangeable. Methods for determining an NRS score are known and may be as described below and/or in the Examples, as applicable. Determining an NRS score comprises the subject providing a numerical rating of their worst itch in the past 24 hours on a scale of "0" being no itch to "10" being the worst imaginable itch. In English, the question posed to the subject is "On a scale of "0" (no itch) to "10" (worst imaginable itch), how was your worst itch in the past 24 hours?". The subject is asked to mark only one number on a scale of 0 to 10.

The mean values of absolute NRS values are calculated per week, i.e. for the corresponding day and the previous 6 days, if at least 4 values are available. For these mean values the absolute change from baseline is calculated. The Baseline value is the value assessed on Day 1. The values from early termination visits are used for the actual day on which the early termination visit was performed.

It is thought that the most appropriate definition of a responder on the Pruritus NRS is in the range of 2 to 4 points.

Baseline scores - NRS: Pruritus / Itch

The atopic dermatitis may have been assessed by determining a baseline NRS score. Determining a baseline NRS score may comprise the subject providing a numerical rating of their worst itch in the past 24 hours on a scale of 0 to 10, wherein "0" is no itch and "10" is the worst imaginable itch. Determining a baseline NRS score may comprise the patient providing a numerical rating of their worst itch in the past 24 hours once per day for 7 days and taking the average numerical rating as the baseline NRS score.

The baseline NRS score may be any score associated with a moderate to severe case of AD. While AD is often associated with itch, NRS does not measure the severity of AD *per se*. It is possible to have severe AD with no itch. However, itch may contribute to the severity of AD, for example, excoriation is a sign assessed when determining an EASI score. NRS may therefore be a relevant descriptor for AD. The baseline NRS score may be selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline NRS score is determined.

Some embodiments may further comprise determining the baseline NRS score.

Clinical outcomes – NRS: Pruritus / Itch

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration NRS (numerical rating scale) score after administering a first injection of the antibody or fragment thereof. Any clinically suitable delay from administration to assessing may be employed. Changes in NRS score have been observed rapidly with, for example, JAKi, and some topical creams may provide instantaneous improvement. The post-administration NRS score may be determined within 2 hours, within 6 hours, within 12 hours, within 24 hours, within 24 hours, or within 7 days of administering a first injection of the antibody or fragment thereof. Although the onset of effect may be measurable more quickly with NRS than with other disease severity measures, the post-administration NRS score may be determined on a similar time scale as one or more other disease severity measure, where this is clinically expedient. The post-administration NRS score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration NRS score may be determined at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration NRS score is determined at the end of the induction phase.

The post-administration NRS score may be 0 to 7. The post-administration NRS score may be reduced at least 1 point, at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the

baseline NRS score. The post-administration NRS score may be reduced at least 3 points or at least 4 points relative to the baseline NRS score. The post-administration NRS score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline NRS score. The post-administration NRS score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration NRS score. The one or more further post-administration NRS score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration NRS score may be determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration NRS score may be determined at the end of the induction phase.

The one or more further post-administration NRS score may be 0 to 7. The one or more further post-administration NRS score may be reduced at least 1 point, at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline NRS score. The one or more further post-administration NRS score may be:

(a) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(b) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

Determining the post-administration NRS score and/or the one or more further post-administration NRS score may comprise the subject providing a numerical rating of their worst itch in the past 24 hours on a scale of 0 to 10, wherein "0" is no itch and "10" is the worst imaginable itch.

The post-administration NRS and/or further post-administration NRS may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS may be:

(a) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(b) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

The post-administration NRS and/or further post-administration NRS may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS may be:

(a) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(b) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

The post-administration NRS and/or further post-administration NRS may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS may be:

(a) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(b) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

The Atopic Dermatitis may be treated as evidenced by a reduction in the NRS score by at least 4 points after the third injection as a treatment dose. The reduction in NRS score may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in NRS score. Some embodiments include therapeutic methods which result in a decrease from baseline in NRS score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later

following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration NRS score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline NRS score. The reduction of the post-administration NRS score relative to the baseline NRS score may be derived from any baseline NRS score and any post-administration NRS score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in NRS score of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in NRS score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Patient Oriented (PO) Eczema Measure (POEM)

The POEM is a seven-item, questionnaire used to assess disease symptoms in children and adults. It is described in Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004 Dec;140(12):1513–9. Methods for determining a POEM score are known and may be as described below and/or in the Examples, as applicable.

Based on frequency of occurrence during the past week, the seven events (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed using a five-point scale. Each of the seven questions carries equal weight and is scored from 0 to 4. The possible scores for each question are: 0 (no days), 1 (1 to 2 days), 2 (3 to 4 days), 3 (5 to 6 days), and 4 (every day). The maximum total score is 28. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are selected, the response option with the highest score should be recorded.

A high score is indicative of poor quality of life. 0 to 2 indicates clear or almost clear skin, 3 to 7 indicates mild eczema, 8 to 16 indicates moderate eczema, 17 to 24 indicates severe eczema, and 25 to 28 indicates very severe eczema. It is thought that the overall mean MCID of the POEM is 3.4 points.

Baseline scores - POEM

The atopic dermatitis may have been assessed by determining a baseline POEM (Patient-Orientated Eczema Measure) score. Determining a baseline POEM score may comprise the subject providing a frequency rating for how often the following events have been caused by their eczema over the last week:

i. Itchy skin,
ii. Disturbed sleep,.
iii. Bleeding skin,
iv. Skin weeping or oozing clear fluid,
v. Cracked skin,
vi. Skin flaking off, and
vii. Skin felt dry or rough.

The frequency rating may be selected from the group consisting of:

i. "no days",
ii. ."1-2 days",
iii. "3-4 days",
iv. "5-6 days", and
v. "every day".

The method may further comprise:

assigning a frequency rating score to each frequency rating, wherein "every day" is assigned a score of 4, "5-6 days" is assigned a score of 3, "3-4 days" is assigned a score of 2, "1-2 days" is assigned a score of 1 and "no days" is assigned a score of 0, and

adding together the frequency rating scores to calculate the POEM score.

A baseline POEM score of 0 to 2 may indicate clear or almost clear eczema; a baseline POEM score of 3 to 7 may indicate mild eczema; a baseline POEM score of 8 to 16 may indicate moderate eczema; a baseline POEM score of 17 to 24 may indicate severe eczema and a baseline POEM score of 25 to 28 may indicate very severe eczema.

The baseline POEM score may be any score indicating moderate to severe or very severe AD. The baseline POEM score may be selected from the group consisting of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at

least 19, at least 20, at least 21, at least 22, at least 23, at least 24, 8 to 28, 8 to 24, 8 to 16, 17 to 24 and 25 to 28.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline POEM score is determined.

Some embodiments may further comprise determining the baseline POEM score.

Clinical outcomes – POEM

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration POEM score at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration POEM score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in POEM score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration POEM score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration POEM score may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration POEM score may be determined at the end of the induction phase.

The post-administration POEM score may be selected from the group consisting of 0 to 2; 3 to 7; 8 to 16; 17 to 24 and 25 to 28. The post-administration POEM score may indicate the AD is no longer very severe AD. The post-administration POEM score may indicate the AD is no longer severe AD. The post-administration POEM score may indicate the AD is no longer moderate AD. The post-administration POEM score may indicate the AD is mild AD. The post-administration POEM score may indicate the AD is almost clear. The post-administration POEM score may be reduced at least 2 points, at least 3 points, at least 3.4 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline POEM score. The post-administration POEM score may be reduced at least 2 points or at least 3 points relative to the baseline POEM score. The post-administration POEM score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline POEM score. The post-administration POEM score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration POEM score. The one or more further post-administration POEM score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration POEM score may be determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration POEM score may be determined at the end of the induction phase.

The one or more further post-administration POEM score may be selected from the group consisting of 0 to 2; 3 to 7; 8 to 16; 17 to 24 and 25 to 28. The one or more further post-administration POEM score may indicate the AD is no longer very severe AD. The one or more further post-administration POEM score may indicate the AD is no longer severe AD. The one or more further post-administration POEM score may indicate the AD is no longer moderate AD. The one or more further post-administration POEM score may indicate the AD is mild AD. The one or more further post-administration POEM score may indicate the AD is almost clear. The one or more further post-administration POEM score may be reduced at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline POEM score. The one or more further post-administration POEM score may be reduced at least 2 points or at least 3 points relative to the baseline POEM score.

Determining the post-administration POEM score and/or the one or more further post-administration POEM score may comprise the subject providing a frequency rating for how often the following events have been caused by their eczema over the last week:

i. Itchy skin,
ii. Disturbed sleep,.
iii. Bleeding skin,
iv. Skin weeping or oozing clear fluid,
v. Cracked skin,
vi. Skin flaking off, and
vii. Skin felt dry or rough.

The frequency rating may be selected from the group consisting of:

i. "no days",
ii. "1-2 days",
iii. "3-4 days",

iv. "5-6 days", and

v. "every day".

The method may further comprise:

assigning a frequency rating score to each frequency rating, wherein "every day" is assigned a score of 4, "5-6 days" is assigned a score of 3, "3-4 days" is assigned a score of 2, "1-2 days" is assigned a score of 1 and "no days" is assigned a score of 0, and

adding together the frequency rating scores to calculate the POEM score.

The post-administration POEM and/or further post-administration POEM may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

The post-administration POEM and/or further post-administration POEM may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

The post-administration POEM and/or further post-administration POEM may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

The Atopic Dermatitis may be treated as evidenced by a reduction in the POEM score by at least 2 points after the third injection as a treatment dose. The reduction in POEM score may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments of, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in POEM score. Some embodiments include therapeutic methods which result in a decrease from baseline in POEM score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration POEM score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline POEM score. The reduction of the post-administration POEM score relative to the baseline POEM score may be derived from any baseline POEM score and any post-administration POEM

score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in POEM score of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in POEM score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Affected body surface area (BSA)

The extent of AD can also be described using BSA. Methods for determining a BSA score are known and may be as described below and/or in the Examples, as applicable. BSA typically uses the "rule of 9's" where body areas are divided into 9% (or fractions thereof) – see Table 2 below. Alternative calculations may be made for children and adults related to different body proportions as indicated in Table 2. Extent by each individual area is calculated and then totalled.

Table 2 – BSA Rule of 9s

Body Part	**Estimated BSA**	
	Adults	**Children**
Entire left arm	9%	9%
Entire right arm	9%	9%
Entire head	9%	18%
Entire chest	9%	9%
Entire abdomen	9%	9%
Entire back	18%	18%
Entire left leg	18%	13.5%
Entire right leg	18%	13.5%

Body Part	Estimated BSA	
	Adults	Children
Groin	1%	1%

BSA or a variant thereof is part of EASI, SCORAD and POSCORAD. BSA in itself can be said not to characterise disease severity *per se*, as a patient can have lots of coverage with low grade disease or have limited coverage with highly severe disease which would be more clinically problematic. Nonetheless, following treatment, a reduction in BSA from baseline may indicate a clinical improvement when AD severity is not increased (optionally measured by an alternative method described herein) in the areas still exhibiting AD involvement.

Baseline scores - BSA

The atopic dermatitis may have been assessed by determining a baseline BSA (Body Surface Area) score. Determining a baseline BSA score may comprise:

(a) Assigning a BSA value to each of the following body parts:

(a) Entire left arm,

(b) Entire right arm,

(c) Entire head,

(d) Entire chest,

(e) Entire abdomen,

(f) Entire back,

(g) Entire left leg,

(h) Entire right leg, and

(i) Groin,

(b) Estimating the proportion of each body part affected by atopic dermatitis,

(c) Multiplying the proportion of each body part affected by dermatitis by the BSA value for the body part to provide an affected BSA value for each body part, and

(d) Adding together the affected BSA values for the body parts to provide a BSA score.

The baseline BSA score may be any score associated with a moderate to severe case of AD. BSA may not measure the severity of AD *per se*. It is possible to have high extent of coverage at low severity levels meaning the overall AD severity may not be very high. However, BSA may contribute to the severity of AD, for example, assigning percentages of body surface area is part of determining an EASI score. BSA may therefore be a relevant descriptor for AD. The baseline BSA score is at least 10%, at least 15, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%,

at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline BSA score is determined.

Some embodiments may further comprise determining the baseline BSA score.

Clinical outcomes – BSA

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration BSA score at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration BSA score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in BSA score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration BSA score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration BSA score may be determined at around 7 days, around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration BSA score may be determined at the end of the induction phase.

The post-administration BSA score may be selected from the group consisting of less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%, less than 85%, less than 90% and less than 95%. The post-administration BSA score may indicate the AD is no longer severe AD. The post-administration BSA score may indicate the AD is no longer moderate AD. The post-administration BSA score may indicate the AD is mild AD. The post-administration BSA score may indicate the AD is almost clear. The post-administration BSA score may be reduced at least 2 percentage points, at least 3 percentage points, at least 4 percentage points, at least 5 percentage points, at least 6 percentage points, at least 7 percentage points, at least 8 percentage points, at least 9 percentage points, 10 percentage points, at least 11 percentage points, at least 12 percentage points, at least 13 percentage points, at least 14 percentage points, at least 15 percentage points, at least 20 percentage points, at least 25 percentage points, at least 30 percentage points, at least 40 percentage points, at least 50 percentage points, at least 60 percentage points, at least 70 percentage points, at least 80 percentage points or at least 90 percentage points relative to the baseline BSA score. The post-administration BSA score may be reduced at least 5 percentage points relative to the baseline BSA score. The post-administration BSA score may be reduced at least 10 percentage points relative to the baseline BSA score, wherein the

baseline BSA score is at least 10%. The post-administration BSA score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline BSA score. The post-administration BSA score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration BSA score. The one or more further post-administration BSA score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration BSA score may be determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration BSA score may be determined at the end of the induction phase.

The one or more further post-administration BSA score may be selected from the group consisting of less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%, less than 85%, less than 90% and less than 95%. The one or more further post-administration BSA score may indicate the AD is no longer severe AD. The one or more further post-administration BSA score may indicate the AD is no longer moderate AD. The one or more further post-administration BSA score may indicate the AD is mild AD. The one or more further post-administration BSA score may indicate the AD is almost clear. The one or more further post-administration BSA score may be reduced at least 2 percentage points, at least 3 percentage points, at least 4 percentage points, at least 5 percentage points, at least 6 percentage points, at least 7 percentage points, at least 8 percentage points, at least 9 percentage points, 10 percentage points, at least 11 percentage points, at least 12 percentage points, at least 13 percentage points, at least 14 percentage points, at least 15 percentage points, at least 20 percentage points, at least 25 percentage points, at least 30 percentage points, at least 40 percentage points, at least 50 percentage points, at least 60 percentage points, at least 70 percentage points, at least 80 percentage points or at least 90 percentage points relative to the baseline BSA score. The one or more further post-administration BSA score may be reduced at least 10 percentage points relative to the baseline BSA score.

Determining the post-administration BSA score and/or the one or more further post-administration BSA score may comprise:

(a) Assigning a BSA value to each of the following body parts:

(a) Entire left arm,

(b) Entire right arm,

(c) Entire head,

(d) Entire chest,

(e) Entire abdomen,

(f) Entire back,

(g) Entire left leg,

(h) Entire right leg, and

(i) Groin,

(b) Estimating the proportion of each body part affected by atopic dermatitis,

(c) Multiplying the proportion of each body part affected by dermatitis by the BSA value for the body part to provide an affected BSA value for each body part, and

(d) Adding together the affected BSA values for the body parts to provide a BSA score.

The post-administration BSA and/or further post-administration BSA may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and the post-administration BSA and/or further post-administration BSA may be reduced at least 10 percentage points relative to the baseline BSA score. The post-administration BSA and/or further post-administration BSA may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and the post-administration BSA and/or further post-administration BSA may be reduced at least 10 percentage points relative to the baseline BSA score. The post-administration BSA and/or further post-administration BSA may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration BSA and/or further post-administration BSA may be reduced at least 10 percentage points relative to the baseline BSA score.

The Atopic Dermatitis may be treated as evidenced by a reduction in the BSA score by at least 10 percentage points after the third injection as a treatment dose. The reduction in BSA score may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments of, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in BSA score. Some embodiments include therapeutic methods which result in a decrease from baseline in BSA score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later

following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration BSA score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline BSA score. The reduction of the post-administration BSA score relative to the baseline BSA score may be derived from any baseline BSA score and any post-administration BSA score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in BSA score of at least 20%, at least 30% or at least 35%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in BSA score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

SCORing of Atopic Dermatitis (SCORAD) Index

The SCORAD was developed to standardize the evaluation of the extent and severity of Atopic Dermatitis. See Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23–31. It assesses three components of AD: the affected BSA, severity of clinical signs, and symptoms.

Methods for determining a SCORAD index are known and may be as described below and/or in the Examples, as applicable.

The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas. The maximum score is 100%. The severity of six specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using a four-point scale (i.e., none = 0, mild = 1, moderate = 2, severe = 3) with a maximum possible total of 18 points. The symptoms (itch and sleeplessness) are recorded by the patient or caregiver on a visual analogue scale, where 0 is no symptoms and 10 is the worst imaginable symptom, with a maximum possible score of 20. The maximum possible SCORAD score is 103; higher scores indicate poorer or more severe condition.

A difference of 8.7 points in SCORAD has been estimated as the minimal clinically important difference (MCID) for patients with atopic dermatitis (Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012 Jan;67(1):99–106).

Baseline scores - SCORAD Index

The atopic dermatitis may have been assessed by determining a baseline SCORAD (SCORing Atopic Dermatitis) index. Determining a baseline SCORAD index may comprise:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) erythema,

(ii) edema/papulation,

(iii) oozing/crust,

(iv) excoriation,

(v) lichenification, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) pruritus, and

(ii) sleep loss;

and

(d) Calculating the baseline SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

Determining a baseline SCORAD index may further comprise assigning to each clinical sign a sign intensity level selected from the group consisting of:

i. "absent"
ii. "mild"
iii. "moderate", and
iv. "severe".

Determining a baseline SCORAD index may further comprise:

assigning a sign intensity score to each sign intensity level, wherein "severe" is assigned a score of 3, "moderate" is assigned a score of 2, "mild" is assigned a score of 1 and "absent" is assigned a score of 0, and

adding together the sign intensity scores to calculate the intensity score "B".

Determining the baseline SCORAD index may comprise the subject or a caregiver providing a numerical rating of symptom severity for pruritus and sleep loss in the past 3 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom. Determining a baseline SCORAD index may further comprise adding together the numerical ratings of symptom severity for pruritus and sleep loss to calculate the severity score "C".

Determining the baseline SCORAD index may comprise calculating the baseline SCORAD index using the formula: SCORAD index = A/5 + 7B/2 + C.

The baseline SCORAD index may be any index indicating moderate to severe AD. A baseline SCORAD index of 0 to 24 may indicate mild disease; a baseline SCORAD index of 25 to 50 may indicate moderate disease; and a baseline SCORAD index of 51 to 103 may indicate severe disease. The baseline SCORAD index may be at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90 or at least 95.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline SCORAD index is determined.

Some embodiments may further comprise determining the baseline SCORAD index.

Based around clinical outcomes – SCORAD

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration SCORAD index at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration SCORAD index at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in SCORAD index could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration SCORAD index may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration SCORAD index may be determined at around 7 days, around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration SCORAD index may be determined at the end of the induction phase.

The post-administration SCORAD index may be selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95. The post-administration SCORAD index may be reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points,

at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline SCORAD index. The post-administration SCORAD index may be reduced at least 20 points relative to the baseline SCORAD index. The post-administration SCORAD index may indicate the AD is no longer very severe AD. The post-administration SCORAD index may indicate the AD is no longer severe AD. The post-administration SCORAD index may indicate the AD is no longer moderate AD. The post-administration SCORAD index may indicate the AD is mild AD. The post-administration SCORAD index may indicate the AD is almost clear. The post-administration SCORAD index may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline SCORAD index. The post-administration SCORAD index may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration SCORAD index. The one or more further post-administration SCORAD index may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration SCORAD index may be determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration SCORAD index may be determined at the end of the induction phase.

The one or more further post-administration SCORAD index may be selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95. The one or more further post-administration SCORAD index may be reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline SCORAD index. The one or more further post-administration SCORAD index may be reduced at least 20 points relative to the baseline SCORAD index. The one or more

further post-administration SCORAD index may indicate the AD is no longer very severe AD. The one or more further post-administration SCORAD index may indicate the AD is no longer severe AD. The one or more further post-administration SCORAD index may indicate the AD is no longer moderate AD. The one or more further post-administration SCORAD index may indicate the AD is mild AD. The one or more further post-administration SCORAD index may indicate the AD is almost clear.

Determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index may comprise:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) erythema,

(ii) edema/papulation,

(iii) oozing/crust,

(iv) excoriation,

(v) lichenification, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) pruritus, and

(ii) sleep loss;

and

(d) Calculating the SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

Determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index may further comprise assigning to each clinical sign a sign intensity level selected from the group consisting of:

i."absent"

ii."mild"

iii."moderate", and

iv."severe".

Determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index may further comprise:

assigning a sign intensity score to each sign intensity level, wherein "severe" is assigned a score of 3, "moderate" is assigned a score of 2, "mild" is assigned a score of 1 and "absent" is assigned a score of 0, and

adding together the sign intensity scores to calculate the intensity score "B".

Determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index may comprise the subject or a caregiver providing a numerical rating of symptom severity for pruritus and sleep loss in the past 3 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom. The method may further comprise adding together the numerical ratings of symptom severity for pruritus and sleep loss to calculate the severity score "C".

Determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index comprises calculating the SCORAD index using the formula: SCORAD index = A/5 + 7B/2 + C.

The post-administration SCORAD and/or further post-administration SCORAD may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD may be reduced at least 20 points relative to the baseline SCORAD index. The post-administration SCORAD and/or further post-administration SCORAD may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD may be reduced at least 20 points relative to the baseline SCORAD index. The post-administration SCORAD and/or further post-administration SCORAD may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD may be reduced at least 20 points relative to the baseline SCORAD index. The Atopic Dermatitis may be treated as evidenced by a reduction in the SCORAD index by at least 20 points after the third injection as a treatment dose. The reduction in SCORAD index may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 monthsafter administration of the last injection as a treatment dose.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in SCORAD index. Some embodiments include therapeutic methods which result in a decrease from baseline in SCORAD index of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration SCORAD index may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline SCORAD index. The reduction of the post-administration SCORAD index relative to the baseline SCORAD index may be derived from any baseline SCORAD index and any post-

administration SCORAD index, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in SCORAD index of at least 20%, at least 30% or at least 35%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in SCORAD index equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Patient Oriented SCORing of Atopic Dermatitis (POSCORAD)

POSCORAD is derived from the SCORAD, and can be easily used by a patient without any particular experience. POSCORAD was created for the patient in order to help patients or caregivers to follow the course of the disease and the effect of the treatment. POSCORAD has been validated in several studies including Vourc'h-Jourdain M, Barbarot S, Taieb A et al. Patient-oriented SCORAD: a self-assessment score in atopic dermatitis. A preliminary feasibility study. Dermatology. 2009;218:246-251 and Stalder JF, Barbarot S, Wollenberg A et al. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. Allergy. 2011;66:1114-1121.

POSCORAD is available as software for mobile devices and computers. A regular (weekly) use of the POSCORAD software allows the patient to create a curve representing the fluctuations of their disease between consultations.

Methods for determining a PO-SCORAD index are known and may be as described below and/or in the Examples, as applicable.

Baseline scores – PO-SCORAD

The atopic dermatitis may have been assessed by determining a baseline PO-SCORAD (Patient-Oriented SCORing Atopic Dermatitis) index. Determining a baseline PO-SCORAD index may comprise:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) redness,

(ii) swelling,

(iii) oozing/scabs,

(iv) scratch marks,

(v) thickening of skin, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) itching, and

(ii) trouble sleeping

and

(d) Calculating the baseline PO-SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

Inputs for steps (a), (b) and (c) may be provided by the subject or a caregiver. Inputs for steps (a), (b) and (c) may be inputted into a computer program via a graphical user interface by the subject or a caregiver. Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A" may be performed by a computer program.

Determining the baseline PO-SCORAD index may comprise the subject or a caregiver providing a sign intensity score for each clinical sign selected from the group consisting of:

i. "0"

ii. "1"

iii. "2", and

iv. "3";

wherein "0" is the lowest intensity and "3" is the highest intensity;

and wherein the sign intensity scores are added together to calculate the intensity score "B". Adding together of the sign intensity scores to calculate the intensity score "B" may be performed by a computer program.

Determining the baseline PO-SCORAD index may comprise the subject or a caregiver providing a numerical rating of symptom severity for itching and trouble sleeping in the past 2 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom. The method may further comprise adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C". Adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C" may be performed by a computer program.

Determining the baseline PO-SCORAD index may comprise calculating the baseline PO-SCORAD index using the formula: PO-SCORAD index = $A/5 + 7B/2 + C$.

The baseline PO-SCORAD index may be any index indicating moderate to severe AD. The baseline PO-SCORAD index may be at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90 or at least 95.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline PO-SCORAD index is determined.

Some embodiments may further comprise determining the baseline PO-SCORAD index.

Based around clinical outcomes – PO-SCORAD

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration PO-SCORAD index at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration PO-SCORAD index at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in PO-SCORAD score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration PO-SCORAD index may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration PO-SCORAD index may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration PO-SCORAD index may be determined at the end of the induction phase.

The post-administration PO-SCORAD index may be selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95. The post-administration PO-SCORAD index may be reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline PO-SCORAD index. The post-administration PO-SCORAD index may be reduced at least 20 points relative to the baseline PO-SCORAD index. The post-administration PO-SCORAD index may indicate the AD is no longer very severe AD. The post-administration PO-SCORAD index may indicate the AD is no longer severe AD. The post-administration PO-SCORAD index may indicate the AD is no longer moderate AD. The post-administration PO-SCORAD index may indicate the AD is mild AD. The post-administration PO-SCORAD index may indicate the AD is almost clear. The post-administration PO-SCORAD index may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%,

at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline PO-SCORAD index. The post-administration PO-SCORAD index may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration PO-SCORAD index. The one or more further post-administration PO-SCORAD index may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration PO-SCORAD index may be determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration PO-SCORAD index may be determined at the end of the induction phase.

The one or more further post-administration PO-SCORAD index is selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95. The one or more further post-administration PO-SCORAD index may be reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline PO-SCORAD index. The one or more further post-administration PO-SCORAD index may be reduced at least 20 points relative to the baseline PO-SCORAD index.

Determining the post-administration PO-SCORAD index and/or the one or more further post-administration PO-SCORAD index may comprise:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) redness,

(ii) swelling,

(iii) oozing/scabs,

(iv) scratch marks,

(v) thickening of skin, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) itching, and

(ii) trouble sleeping;

and

(d) Calculating the PO-SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

Inputs for steps (a), (b) and (c) may be provided by the subject or a caregiver. Inputs for steps (a), (b) and (c) may be inputted into a computer program via a graphical user interface by the subject or a caregiver. Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A" may be performed by a computer program.

Determining the post-administration PO-SCORAD index may comprise the subject or a caregiver providing a sign intensity score for each clinical sign selected from the group consisting of:

i. "0"

ii. "1"

iii. "2", and

iv. "3";

wherein "0" is the lowest intensity and "3" is the highest intensity;

and wherein the sign intensity scores are added together to calculate the intensity score "B". The adding together of the sign intensity scores to calculate the intensity score "B" may be performed by a computer program.

Determining the post-administration PO-SCORAD index may comprise the subject or a caregiver providing a numerical rating of symptom severity for itching and trouble sleeping in the past 2 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom. The method may further comprise adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C". Adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C" may be performed by a computer program.

Determining the post-administration PO-SCORAD index and/or the one or more further post-administration PO-SCORAD index may comprise calculating the PO-SCORAD index using the formula: PO-SCORAD index = A/5 + 7B/2 + C.

The post-administration PO-SCORAD and/or further post-administration PO-SCORAD may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration PO-SCORAD and/or further post-administration PO-

SCORAD may be reduced at least 20 points relative to the baseline PO-SCORAD index. The post-administration PO-SCORAD and/or further post-administration PO-SCORAD may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD may be reduced at least 20 points relative to the baseline PO-SCORAD index. The post-administration PO-SCORAD and/or further post-administration PO-SCORAD may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD may be reduced at least 20 points relative to the baseline PO-SCORAD index. The Atopic Dermatitis may be treated as evidenced by a reduction in the PO-SCORAD index by at least 20 points after the third injection as a treatment dose. The reduction in PO-SCORAD index may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose. According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in PO-SCORAD index. In some embodiments, the therapeutic methods which result in a decrease from baseline in PO-SCORAD index of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration PO-SCORAD index may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline PO-SCORAD index. The reduction of the post-administration PO-SCORAD index relative to the baseline PO-SCORAD index may be derived from any baseline PO-SCORAD index and any post-administration PO-SCORAD index, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in PO-SCORAD index of at least 15%, at least 20% or at least 30%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in PO-SCORAD index equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

Dermatology Life Quality Index (DLQI)

The DLQI is designed to measure the health-related quality of life of patients suffering from a skin disease, including Atopic Dermatitis. The DLQI was published in 1994 and was the first dermatology-specific quality of life questionnaire. See Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994 May;19(3):210–6. Methods for determining a DQLI score are known and may be as described below and/or in the Examples, as applicable.

The DLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. The DLQI is designed for use in adults, i.e. patients aged 16 years and over.

Each question is scored on a four-point Likert scale:

Very much = 3

A lot = 2

A little = 1

Not at all = 0

Not relevant = 0

Question unanswered = 0

The DLQI is calculated by adding the score of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. A score higher than 10 indicates that the patient's life is being severely affected by their skin disease.

Meaning of scores:

- 0-1 = no effect at all on patient's life
- 2-5 = small effect on patient's life
- 6-10 = moderate effect on patient's life
- 11-20 = very large effect on patient's life
- 21-30 = extremely large effect on patient's life

For general inflammatory skin conditions, a change in DLQI score of at least four points is considered clinically important. In alternative embodiments, a change in DLQI score of from 2.2 to 6.9 points is considered clinically important.

Baseline *scores - DQLI*

The atopic dermatitis may have been assessed by determining a baseline DQLI (Dermatology Quality of Life Index) score. Determining a baseline DQLI score may comprise the subject providing

an answer for how much their skin problem has affected their life over the past week in the following areas:

i. how itchy, sore, painful or stinging their skin has been,
ii. how embarrassed or self conscious they have been because of their skin,
iii. how much their skin has interfered with them going shopping or looking after their home or garden,
iv. how much their skin has influenced the clothes they wear,
v. how much their skin has affected any social or leisure activities,
vi. how much their skin has made it difficult to do any sport
vii. whether their skin has prevented them from working or studying or if not how much their skin has been a problem at work or studying,
viii. how much their skin has created problems with their partner of any of their close friends or relatives,
ix. how much their skin has caused any sexual difficulties
x. how much of a problem has the treatment for their skin been.

Each answer may be selected from the group consisting of:

i. "Very much"
ii. "A lot"
iii. "A little"
iv. "Not at all"
v. "Not relevant"

The method may further comprise:

assigning an answer score to each answer, wherein "very much" is assigned a score of 3, "a lot" is assigned a score of 2, "a little" is assigned a score of 1 and "not at all", "not relevant" or question unanswered are assigned a score of 0, and

adding together the answer scores to calculate a DQLI score.

The baseline DQLI index may be any index indicating AD is having a moderate effect, a large effect or an extremely large effect on the subject's life. The baseline DQLI score may be selected from the group consisting of at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, 6 to 30, 6 to 10, 11 to 20, and 21 to 30.

A first injection of the anti-OX40L antibody or fragment thereof may be administered on the same day as the baseline DQLI score is determined.

Some embodiments may further comprise determining the baseline DQLI score.

Based around clinical outcomes – DQLI

Some embodiments may further comprise assessing the atopic dermatitis by determining a post-administration DQLI score at least 15 days after administering a first injection of the antibody or fragment thereof. Obtaining a post-administration DQLI score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof is expected to be the earliest a change in DQLI score could reliably be observed due to the action of the antibody or fragment thereof, however any clinically suitable delay from administration to assessing may be employed. The post-administration DQLI score may be determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration DQLI score may be determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof. The post-administration DQLI score may be determined at the end of the induction phase.

The post-administration DQLI score may be selected from the group consisting of 0 to 1; 2 to 5; 6 to 10; 11 to 20; and 21 to 30. The post-administration DQLI score may be reduced at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 15 points or at least 20 points relative to the baseline DQLI score. The post-administration DQLI score may be reduced at least 2.2 points or at least 6.9 points relative to the baseline DQLI score. The post-administration DQLI score may be reduced at least 4 points relative to the baseline DQLI score. The post-administration DQLI score may be reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline DQLI score. The post-administration DQLI score may be maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

Some embodiments may further comprise assessing the atopic dermatitis by determining one or more further post-administration DQLI score. The one or more further post-administration DQLI score may be determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof. The one or more further post-administration DQLI score may be determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days

after administering a first injection of the antibody or fragment thereof. The one or more further post-administration DQLI score may be determined at the end of the induction phase.

The one or more further post-administration DQLI score may be selected from the group consisting of 0 to 1; 2 to 5; 6 to 10; 11 to 20; and 21 to 30. The one or more further post-administration DQLI score may be reduced at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 15 points or at least 20 points relative to the baseline DQLI score. The one or more further post-administration DQLI score may be reduced at least 2.2 points or at least 6.9 points relative to the baseline DQLI score. The one or more further post-administration DQLI score may be reduced at least 4 points relative to the baseline DQLI score.

Determining the post-administration DQLI score and/or the one or more further post-administration DQLI score may comprise the subject providing an answer for how much their skin problem has affected their life over the past week in the following areas:

i. how itchy, sore, painful or stinging their skin has been,
ii. how embarrassed or self conscious they have been because of their skin,
iii. how much their skin has interfered with them going shopping or looking after their home or garden,
iv. how much their skin has influenced the clothes they wear,
v. how much their skin has affected any social or leisure activities,
vi. how much their skin has made it difficult to do any sport
vii. whether their skin has prevented them from working or studying or if not how much their skin has been a problem at work or studying,
viii. how much their skin has created problems with their partner of any of their close friends or relatives,
ix. how much their skin has caused any sexual difficulties
x. how much of a problem has the treatment for their skin been.

Each answer may be selected from the group consisting of:

i. "Very much"
ii. "A lot"
iii. "A little"
iv. "Not at all"
v. "Not relevant"

The method may further comprise:

assigning an answer score to each answer, wherein "very much" is assigned a score of 3, "a lot" is assigned a score of 2, "a little" is assigned a score of 1 and "not at all", "not relevant" or question unanswered are assigned a score of 0, and

adding together the answer scores to calculate a DQLI score.

The post-administration DQLI score and/or further post-administration DQLI score may be determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score may be reduced at least 4 points relative to the baseline DQLI score. The post-administration DQLI score and/or further post-administration DQLI score may be determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score may be reduced at least 4 points relative to the baseline DQLI score. The post-administration DQLI score and/or further post-administration DQLI score may be determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score may be reduced at least 4 points relative to the baseline DQLI score. The Atopic Dermatitis may be treated as evidenced by a reduction in the DQLI score by at least 4 points after the third injection as a treatment dose. The reduction in DQLI score may be persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

According to certain embodiments of, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in DQLI score. Some embodiments include therapeutic methods which result in a decrease from baseline in DQLI score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof). The post-administration DQLI score may be reduced at least at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline DQLI score. The reduction of the post-administration DQLI score relative to the baseline DQLI score may be derived from any baseline DQLI score and any post-administration DQLI score, at any time point or between any time points, disclosed herein. In certain exemplary embodiments, administration of an anti-OX40L antibody, or antigen-binding fragment thereof to a subject results in a decrease from baseline in DQLI score of at least 20%, at least 30% or at least 35%, optionally at around day 113 after the first administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, administration of a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to a patient results in a decrease in DQLI score equal to or greater than the minimal clinically important difference (MCID), at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169, 253 or later following administration of the anti-OX40L

antibody, or antigen-binding fragment thereof (e.g., following subcutaneous administration of about 62.5 mg, 125 mg, 250 mg or a 500mg loading dose followed by 250 mg of an anti-OX40L antibody, or antigen-binding fragment thereof).

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Population level clinical effects

The advantageous effects of some embodiments may be described on a population level, that is considering the effects across multiple subjects, such as average effects. The effects on a population level may be relative to a control. The control may be placebo. The control may be untreated patients. The control may be a baseline, such as an average of subject baselines obtained before treatment. Effects of some embodiments may include:

- At least a 35% improvement in the proportion of patients achieving IGA-AD 0/1 at assessment. The improvement may be seen at an assessment conducted around 16 weeks after administering the first dose.
- A further around 5% improvement in the proportion of patients achieving IGA-AD 0/1 at a further assessment. The improvement may be seen at an assessment conducted around 16 weeks to 24 weeks after administering the first dose.
- At least a 40% improvement in the proportion of patients achieving EASI75 at assessment. The improvement may be seen at an assessment conducted around 16 weeks after administering the first dose.
- A further around 10% improvement in the proportion of patients achieving EASI75 at a further assessment. The improvement may be seen at an assessment conducted around 16 weeks to 24 weeks after administering the first dose.
- At least a 35% improvement in the proportion of patients achieving EASI90 at assessment. The improvement may be seen at an assessment conducted around 16 weeks after administering the first dose.
- A further around 5% improvement in the proportion of patients achieving EASI90 at a further assessment. The improvement may be seen at an assessment conducted around 24 weeks after administering the first dose.
- At least a ≥ 25% improvement in the proportion of patients achieving at least a 4-point improvement in Pruritus NRS score at assessment. The improvement may be seen at an assessment conducted around 16 weeks after administering the first dose.
- A further around 5% improvement in the proportion of patients achieving at least a 4-point improvement in Pruritus NRS at assessment. The improvement may be seen at an assessment conducted around 24 weeks after administering the first dose.

- A reduction in the EASI score by at least 40% after a third treatment dose and wherein the reduction in EASI score is persistent for at least 2 months after administration of the last dose.

Any one or more of the above effects may be taken as evidence that the Atopic Dermatitis has been treated.

Another embodiment is related to a method of treating atopic dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in at least one improvement selected from the group consisting of:

a. a decrease from baseline in vIGA score of at least 2 points, or
b. achieving clear or almost clear skin (vIGA0/1) from baseline.

Another embodiment is related to a method of treating atopic dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in at least one improvement selected from the group consisting of:

a. a decrease from baseline in EASI score of at least 50%, or
b. a decrease from baseline in EASI score of at least 75%, or
c. achieving EASI-75, or
d. achieving EASI-90, or
e. achieve at least 3 points a pruritus NRS, or
f. achieve at least 4 points a pruritus NRS, or
g. a decrease from baseline in SCORAD Index of at least 50%, or
h. a decrease from baseline in SCORAD Index of at least 55%, or
i. a decrease from baseline in affected BSA of at least 60%
j. a decrease from baseline in affected BSA of at least 70%

Another embodiment is related to a method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disorder, atopic dermatitis or moderate-to-severe atopic dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in the decrease in serum levels of at least one biomarker selected from the group consisting of: IL-13, IL-22, IL-17A, IL-31 and IgE.

According to certain embodiment of the above-mentioned methods, at least one of the improvements is achieved at week 16. According to certain embodiment of the above-mentioned methods, at least one of the improvements is maintained for at least 12 weeks or at least 24 weeks following the final dose.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Administration to children

Atopic Dermatitis may develop in early childhood. Children therefore represent an important group for treatment. Patient bodyweight may be accounted for in dosing, so doses administered to children may be lower than those administered to adults. The subject may be aged from 12 to 18 years old. The subject may have an age of 6 months to 11 years. The subject may have an age of 12 years to 17 years.

Depending on the dose used, the antibody or fragment thereof may be administered either intravenously or subcutaneously based on the judgment of a clinician who will determine which route of administration is best for their patient accounting for their bodyweight.

Formulations

IV and SC formulations of anti-OX40L antibodies, such as KY1005 have been found to exhibit surprisingly consistent pharmacokinetic (PK) parameter estimates in IV and subcutaneous population PK models. One advantage observed is a linear PK (with the exception of some non-linearity seen in low doses, such as around 0.45 mg/kg, in healthy subjects), allowing the PK model to be described as a "linear two compartment distribution model", for both IV and subcutaneous administration. Here, the term "linear" refers to the clearance – encompassing the rate of clearance (CL) and the rate of clearance from the central compartment to the second compartment (Q1) – both of which are shown to be linear in the data disclosed herein. The same finding applies in both AD and healthy patients. Without being bound by theory, this may be related to a low expression of OX40L, such that the rate of clearance does not change based on concentration of drug (or therefore time).

IV and SC formulations of anti-OX40L antibodies, such as KY1005 have been found to exhibit surprisingly low immunogenicity. One component of a harmful immune response to a therapeutic protein is the formation of anti-drug antibodies (ADA). The consequences of an immune reaction to a therapeutic protein range from transient appearance of ADAs without any clinical significance to severe life-threatening conditions. Potential clinical consequences of an unwanted immune response include loss of efficacy of the therapeutic protein and serious acute immune effects such as anaphylaxis. ADAs

can affect efficacy of a therapeutic protein either by interfering with the pharmacodynamic interaction between the therapeutic protein and its target or by altering its pharmacokinetic profile.

As described in the European Medicines Agency (EMA) Guideline on Immunogenicity assessment of therapeutic proteins (18 May 2017, EMEA/CHMP/BMWP/42832/2005 Rev1, Committee for Medicinal Products for Human Use (CHMP)), products given intravenously may be less immunogenic than drugs given subcutaneously. It is therefore surprising that the population PK profile formulations of anti-OX40L antibodies, such as KY1005 are so similar between IV and subcutaneous administration scenarios (based on a single subcutaneous dose). No meaningful effect of ADA is apparent from the data disclosed herein.

In some embodiments, the IV and SC formulations of anti-OX40L antibodies, such as KY1005 are formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol. 52:238-311.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Products

A liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof may be contained in a medical container, e.g., a vial, syringe, IV container or an injection device (e.g., a subcutaneous injection device). In an example, the liquid formulation comprising the anti-OX40L antibody, or antigen-binding fragment thereof is *in vitro*,.e.g., in a sterile container.

Some embodiments therefore also provides:

- A glass vial containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.
- A drug delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.
- A prefilled syringe containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.
- A microinfusor containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.
- A pen delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof. The pen delivery device may be a reusable pen delivery device. The pen delivery device may be a disposable pen delivery device.

- An autoinjector delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

An example drug delivery device may involve a needle-based injection system as described in Table 1 of section 5.2 of ISO 11608-1:2014(E). As described in ISO 11608-1:2014(E), needle-based injection systems may be broadly distinguished into multi-dose container systems and single-dose (with partial or full evacuation) container systems. The container may be a replaceable container or an integrated non-replaceable container.

As further described in ISO 11608-1:2014(E), a multi-dose container system may involve a needle-based injection device with a replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user). Another multi-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).

As further described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with a replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation). As also described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation).

In some embodiments, he glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device or autoinjector may contain a volume of a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof is up to 1 mL, up to 2 mL or up to 2.25 mL.

In some embodiments, a kit comprising a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device or autoinjector; and a label and/or instructions specifying administration in accordance with some embodiments,optionally wherein the label or instructions comprise a marketing authorisation number (e.g., an FDA or EMA authorisation number). In an example, is provided a kit comprising a liquid formulation comprising the anti-OX40L antibody, or antigen-binding fragment thereof, packaging and instructions for use in treating Atopic Dermatitis. In an example, the human is of Chinese (e.g., Han or CHS) ethnicity and the instructions are in Chinese (e.g., Mandarin).

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Formulations & Products in method

In some embodiments, he products may be used in embodiments of the described methods.

In some embodiments is provided a method, wherein the antibody or fragment thereof is administered from a prefilled syringe, a microinfusor, a pen delivery device or an autoinjector delivery device.

In some embodiments is provided a method, wherein the antibody or fragment thereof is administered from a prefilled syringe.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Medical uses

Embodiments of the invention also provides the following medical uses:

- An anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating Atopic Dermatitis in accordance with some embodiments of the method.
- A glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit, for use in a method of treating Atopic Dermatitis in accordance with some embodiments of the method.
- The use of an anti-OX40L antibody, or antigen-binding fragment thereof, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with some embodiments of the method.
- The use of a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with some embodiments of the method.
- In any of the above medical uses, the Atopic Dermatitis may be Chronic Atopic Dermatitis.

Some embodiments also provides the following medical uses: inflammatory diseases, inflammatory disorders, immune-mediated diseases, immune-mediated disorders, inflammatory skin diseases or inflammatory skin disorders.

Some embodiments also provides the following medical uses: inflammatory diseases, inflammatory disorders, immune-mediated diseases, immune-mediated disorders, inflammatory skin diseases or inflammatory skin disorders in both Th2 and non-Th2 patient populations or patient populations having mixed phenotype or patient with mixed inflammatory responses. The invention also provides the following medical uses: inflammatory diseases, inflammatory disorders, immune-mediated diseases, immune-mediated disorders, inflammatory skin diseases or inflammatory skin

disorders in Th2 patient populations, non-Th2 patient populations, high Th2 patient populations, low Th2 patient populations or non Th2 patient populations.

Some embodiments also provides the following medical uses: inflammatory diseases, inflammatory disorders, immune-mediated diseases, immune-mediated disorders, inflammatory skin diseases or inflammatory skin disorders in both Type 2 and non-Type 2 patient populations or patient populations having mixed phenotype or patient with mixed inflammatory responses. The invention also provides the following medical uses: inflammatory diseases, inflammatory disorders, immune-mediated diseases, immune-mediated disorders, inflammatory skin diseases or inflammatory skin disorders in Type 2 patient populations, non-Type 2 patient populations, high Type 2 patient populations, low Type 2 patient populations or non-Type 2 patient populations.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.Antibodies

In some embodiments, antibodies include, but are not limited to, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, multispecific antibodies (including bi-specific antibodies), human antibodies, humanized antibodies, chimeric antibodies, intrabodies, single-chain Fvs (scFv) (e.g., including monospecific, bispecific, etc.), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

In particular, antibodies provided herein include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds to a hOX40L antigen. The immunoglobulin molecules provided herein can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In a specific embodiment, an antibody provided herein is an IgG antibody, preferably an IgG1 or IgG4. In certain embodiments, the antibodies comprise a human gamma 4 constant region. In another embodiment, the heavy chain constant region does not bind Fc-γ receptors, and e.g. comprises a Leu235Glu mutation. In another embodiment, the heavy chain constant region comprises a Ser228Pro mutation to increase stability. In another embodiment, the heavy chain constant region is IgG4-PE.

Variants and derivatives of antibodies include antibody fragments that retain the ability to specifically bind to an epitope. In some embodiments the fragments include Fab fragments; Fab' (an antibody fragment containing a single anti-binding domain comprising an Fab and an additional portion of the heavy chain through the hinge region); $F(ab')_2$ (two Fab' molecules joined by interchain disulfide bonds in the hinge regions of the heavy chains; the Fab' molecules may be directed toward the same or different epitopes); a bispecific Fab (a Fab molecule having two antigen binding domains, each of which may be directed to a different epitope); a single chain Fab chain comprising a variable region, also known as, a sFv; a disulfide-linked Fv, or dsFv; a camelized VH (the variable, antigen-binding

determinative region of a single heavy chain of an antibody in which some amino acids at the VH interface are those found in the heavy chain of naturally occurring camel antibodies); a bispecific sFv (a sFv or a dsFv molecule having two antigen-binding domains, each of which may be directed to a different epitope); a diabody (a dimerized sFv formed when the VH domain of a first sFv assembles with the VL domain of a second sFv and the VL domain of the first sFv assembles with the VH domain of the second sFv; the two antigen-binding regions of the diabody may be directed towards the same or different epitopes); and a triabody (a trimerized sFv, formed in a manner similar to a diabody, but in which three antigen-binding domains are created in a single complex; the three antigen binding domains may be directed towards the same or different epitopes). Derivatives of antibodies also include one or more CDR sequences of an antibody combining site. The CDR sequences may be linked together on a scaffold when two or more CDR sequences are present. In certain embodiments, the antibody comprises a single-chain Fv ("scFv"). scFvs are antibody fragments comprising the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFvs see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, New York, pp. 269-315 (1994).

In some embodiments, the antibodies may be from any animal origin including birds and mammals (e.g., human, murine, donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken). In certain embodiments, the antibodies of the invention are human or humanized monoclonal antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from mice that express antibodies from human genes.

In some embodiments, the antibodies are fully human antibodies, such as fully human antibodies that specifically bind a hOX40L polypeptide, a hOX40L polypeptide fragment, or a hOX40L epitope. Such fully human antibodies would be advantageous over fully mouse (or other full or partial non-human species antibodies), humanized antibodies, or chimeric antibodies to minimize the development of unwanted or unneeded side effects, such as immune responses directed toward non-fully human antibodies (e.g., anti-hOX40L antibodies derived from other species) when administered to the subject.

In some embodiments, the antibodies may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a hOX40L polypeptide or may be specific for both a hOX40L polypeptide as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. In some embodiments, the antibodies provided herein are monospecific for a given epitope of a hOX40L polypeptide and do not specifically bind to other epitopes.

Also provided herein is a B-cell (e.g., an immortalised B-cell) or a hybridoma that produces an anti-hOX40L antibody or fragment described herein.

In certain embodiments, an isolated antibody is provided herein that specifically binds to a hOX40L epitope wherein the binding to the hOX40L epitope by the antibody is competitively blocked (,, in a dose-dependent manner) by an antibody or fragment. The antibody may or may not be a fully human antibody. In some embodiments, the antibody is a fully human monoclonal anti-hOX40L antibody, and even more preferably a fully human, monoclonal, antagonist anti-hOX40L antibody. Exemplary competitive blocking tests that can be used are provided in the Examples herein.

In some embodiments, the antibody or fragment competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to cell surface-expressed hOX40L. In other embodiments, the antibody or fragment competes (e.g., in a dose-dependent manner) with OX40 Receptor (or a fusion protein thereof) for binding to soluble hOX40L. Exemplary competitive binding assays that can be used are provided in the Examples herein. In one embodiment, the antibody or fragment partially or completely inhibits binding of hOX40 to cell surface-expressed OX40L, such as hOX40L. In another embodiment, the antibody partially or completely inhibits binding of hOX40 to soluble hOX40L. In some embodiments, the antibody or fragment partially or completely inhibits the secretion of CCL20, IL-8, and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ from a cell having cell surface-expressed OX40. In certain embodiments, the cell expressing the OX40 is a colonic epithelial cell.

In some embodiments, the antibodies are fully human, monoclonal antibodies, such as fully human, monoclonal antagonist antibodies, that specifically bind to hOX40L. In some embodiments, the antibodies are OX40L antagonist antibodies. In some embodiments, the antibodies are fully human, monoclonal antibodies, such as fully human, monoclonal OX40L antagonist antibodies.

In some embodiments, the antibody or fragment provided herein binds to a hOX40L epitope that is a three-dimensional surface feature of a hOX40L polypeptide (e.g., in a trimeric form of a hOX40L polypeptide). A region of a hOX40L polypeptide contributing to an epitope may be contiguous amino acids of the polypeptide or the epitope may come together from two or more non-contiguous regions of the polypeptide A hOX40L epitope may be present in (a) the trimeric form ("a trimeric hOX40L epitope") of hOX40L, (b) the monomeric form ("a monomeric hOX40L epitope") of hOX40L, (c) both the trimeric and monomeric form of hOX40L, (d) the trimeric form, but not the monomeric form of hOX40L, or (e) the monomeric form, but not the trimeric form of hOX40L.

For example, in some embodiments, the epitope is only present or available for binding in the trimeric (native) form, but is not present or available for binding in the monomeric (denatured) form by an anti-hOX40L antibody. In other embodiments, the hOX40L epitope is linear feature of the hOX40L polypeptide (e.g., in a trimeric form or monomeric form of the hOX40L polypeptide). Antibodies provided herein may specifically bind to (a) an epitope of the monomeric form of hOX40L, (b) an epitope of the trimeric form of hOX40L, (c) an epitope of the monomeric but not the trimeric

form of hOX40L, (d) an epitope of the trimeric but not the monomeric form of hOX40L, or (e) both the monomeric form and the trimeric form of hOX40L. In some embodiments, the antibodies provided herein specifically bind to an epitope of the trimeric form of hOX40L but do not specifically bind to an epitope the monomeric form of hOX40L.

Some embodiments also provide antibodies that specifically bind to a hOX40L epitope, the antibodies comprising derivatives of the VH domains, VH CDRs, VL domains, and VL CDRs described herein that specifically bind to a hOX40L antigen. Some embodiments also provide antibodies comprising derivatives of antibodies disclosed in the Examples, wherein said antibodies specifically bind to a hOX40L epitope. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which results in amino acid substitutions. Preferably, the derivatives include less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the original molecule. In another embodiment, the derivatives have conservative amino acid substitutions. In a some embodiments, the derivatives have conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed and the activity of the protein can be determined.

In another embodiment, an antibody that specifically binds to a hOX40L epitope comprises a variable domain amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to a variable domain amino acid sequence of the sequence listing.

In specific embodiments, the antibody is a fully human anti-human antibody, such as a fully human monoclonal antibody. Fully human antibodies may be produced by any method known in the art. Exemplary methods include immunization with a hOX40L antigen (any hOX40L polypeptide capable of eliciting an immune response, and optionally conjugated to a carrier) of transgenic animals (e.g., mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production; see, e.g., Jakobovits *et al.*, (1993) Proc. Natl. Acad. Sci., 90:2551; Jakobovits *et al.*, (1993) Nature, 362:255 258 (1993); Bruggermann *et al.*, (1993) Year in Immunol., 7:33. Other methods of producing fully human anti-hOX40L antibodies can be found in the Examples provided herein.

Alternatively, fully human antibodies may be generated through the in vitro screening of phage display antibody libraries; see e.g., Hoogenboom *et al.*, J. Mol. Biol., 227:381 (1991); Marks *et al.*, J.

Mol. Biol., 222:581 (1991), incorporated herein by reference. Various antibody-containing phage display libraries have been described and may be readily prepared by one skilled in the art. Libraries may contain a diversity of human antibody sequences, such as human Fab, Fv, and scFv fragments, that may be screened against an appropriate target.

In some embodiments, the antibodies and fragments include antibodies and fragments that are chemically modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been chemically modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formulation, metabolic synthesis of tunicamycin, etc. Additionally, the antibody may contain one or more non-classical amino acids.

Some embodiments also provide antibodies that specifically bind to a hOX40L antigen which comprise a framework region known to those of skill in the art (e.g., a human or non-human fragment). The framework region may, for example, be naturally occurring or consensus framework regions. In some embodiments, the framework region of an antibody is human (see, e.g., Chothia *et al.*, 1998, J. Mol. Biol. 278:457-479 for a listing of human framework regions, which is incorporated by reference herein in its entirety). See also Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest (U.S. Department of Health and Human Services, Washington, D.C.) 5th ed.

Some embodiments, provide for antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of one or more of the CDRs in the sequence listing (i.e. Seq ID No:4, Seq ID No:10, Seq ID No:36, Seq ID No:42, Seq ID No:68, Seq ID No:74, Seq ID No:96 or Seq ID No:102, in particular, Seq ID No:36 or Seq ID No:42 for HCDR1; Seq ID No:6, Seq ID No:12, Seq ID No:38, Seq ID No:44, Seq ID No:70, Seq ID No:76, Seq ID No:98 or Seq ID No:104, in particular Seq ID No:38 or Seq ID No:44 for HCDR2; Seq ID No:8, Seq ID No:14, Seq ID No:40, Seq ID No:46, Seq ID No:72, Seq ID No:78, Seq ID No:100 or Seq ID No:106, in particular Seq ID No:40 or Seq ID No:46 for HCDR3; Seq ID No:18, Seq ID No:24, Seq ID No:50, Seq ID No:56, Seq ID No:82, Seq ID No:88, Seq ID No:110 or Seq ID No:116, in particular Seq ID No:50 or Seq ID No:56 for LCDR1; Seq ID No:20, Seq ID No:26, Seq ID No:52, Seq ID No:58, Seq ID No:84, Seq ID No:90, Seq ID No:112 or Seq ID No:118, in particular Seq ID No:52 or Seq ID No:58 for LCDR2; and Seq ID No:22, Seq ID No:28, Seq ID No:54, Seq ID No:60, Seq ID No:86, Seq ID No:92, Seq ID No:114 or Seq ID No:120, in particular Seq ID No:54 or Seq ID No:60 for LCDR3) and human framework regions with one or more amino acid substitutions at one, two, three or more of the following residues: (a) rare framework residues that differ between the murine antibody framework (i.e., donor antibody framework) and the human antibody framework (i.e., acceptor antibody framework); (b) Vernier zone residues when differing between donor antibody framework and acceptor antibody framework; (c)

interchain packing residues at the VH/VL interface that differ between the donor antibody framework and the acceptor antibody framework; (d) canonical residues which differ between the donor antibody framework and the acceptor antibody framework sequences, particularly the framework regions crucial for the definition of the canonical class of the murine antibody CDR loops; (e) residues that are adjacent to a CDR; (g) residues capable of interacting with the antigen; (h) residues capable of interacting with the CDR; and (i) contact residues between the VH domain and the VL domain. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprising the human framework regions with one or more amino acid substitutions at one, two, three or more of the above-identified residues are antagonistic hOX40L antibodies.

Some embodiments encompass antibodies that specifically bind to a hOX40L antigen, said antibodies comprising the amino acid sequence of the VH domain and/or VL domain in the sequence listing (i.e. Seq ID No:2, Seq ID No:34, Seq ID No:66 or Seq ID No:94, in particular Seq ID No:34 for VH domains; Seq ID No:16, Seq ID No:48, Seq ID No:80, or Seq ID No:108, in particular Seq ID No:48 for VL domains) but having mutations (e.g., one or more amino acid substitutions) in the framework regions. In certain embodiments, antibodies that specifically bind to a hOX40L antigen comprise the amino acid sequence of the VH domain and/or VL domain or an antigen-binding fragment thereof of an antibody disclosed in the Examples with one or more amino acid residue substitutions in the framework regions of the VH and/or VL domains.

In some embodiments, antibodies provided herein decrease or inhibit binding of hOX40L hOX40, and/or decrease or inhibit a hOX40L biological activity, such as secretion of CCL20, IL8 and/or RANTES , or INF-γ, TNF-α or IL-2, in particular INF-γ, in subject (e.g., a human subject). In certain embodiments, antibodies provided herein, such as a human monoclonal anti-hOX40L antibody, decreases or inhibits binding of a soluble or cell-surface expressed hOX40L to hOX40, and/or decreases or inhibits secretion of CCL20 and/or RANTES, or INF-γ, TNF-α or IL-2, in particular INF-γ after contact with a soluble or cell-surface expressed hOX40L, in a subject. Blocking activity of an antibody provided herein of hOX40L binding to hOX40 can be detected using an assay as described in the Examples. Inhibition of biological activity of cells expressing OX40 by a hOX40L antibody provided herein can be detected using an assay as described in the Examples.

Some embodiments also provide for fusion proteins comprising an antibody provided herein that specifically binds to a hOX40L antigen and a heterologous polypeptide. In some embodiments, the heterologous polypeptide to which the antibody is fused is useful for targeting the antibody to cells having cell surface-expressed hOX40L.

Optionally, the antibody or fragment specifically binds hOX40L with an affinity (apparent affinity, Kd) of less than 1 mM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1mM to 1pM (e.g., 1mM to 100pM; 10nM to 100pM; 1nM to 10pM; or 100pM to 1pM) as determined by SPR, e.g., under SPR conditions disclosed herein).

Additionally or alternatively, the antibody or fragment specifically binds rhesus monkey OX40L with an affinity (apparent affinity, Kd) of less than 1 microM, 1000 nM to 100 nM, 100 nM to 10 nM, 10 nM to 1 nM, 1000 pM to 500 pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM, e.g., in the range of 1mM to 1pM (e.g., 1mM to 100pM; 10nM to 100pM; 1nM to 10pM; or 100pM to 1pM) as determined by SPR, e.g., under SPR conditions disclosed herein). Such binding measurements can be made using a variety of binding assays known in the art, e.g., using surface plasmon resonance (SPR), such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®), using KinExA® (Sapidyne Instruments, Inc), or using ForteBio Octet (Pall ForteBio Corp.).

OX40L binding ability, specificity and affinity (K_D, k_{off} and/or k_{on}) can be determined by any routine method in the art, e.g., by surface plasmon resonance (SPR). The term "k_{on}" or "k_a" as used herein refers to the association constant. The term "k_d" or "k_{off}" as used herein refers to the dissociation constant. The term "K_D", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction. Such binding measurements can be made using a variety of binding assays known in the art, e.g., using surface plasmon resonance (SPR), such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®), using KinExA® (Sapidyne Instruments, Inc), or using ForteBio Octet (Pall ForteBio Corp.).

In one embodiment, the surface plasmon resonance (SPR) is carried out at 25°C. In another embodiment, the SPR is carried out at 37°C.

In one embodiment, the SPR is carried out at physiological pH, such as about pH7 or at pH7.6 (e.g., using Hepes buffered saline at pH7.6 (also referred to as HBS-EP)).

In one embodiment, the SPR is carried out at a physiological salt level, e.g., 150mM NaCl.

In one embodiment, the SPR is carried out at a detergent level of no greater than 0.05% by volume, e.g., in the presence of P20 (polysorbate 20; e.g., Tween-20™) at 0.05% and EDTA at 3mM.

In one example, the SPR is carried out at 25°C or 37°C in a buffer at pH7.6, 150mM NaCl, 0.05% detergent (e.g., P20) and 3mM EDTA. The buffer can contain 10mM Hepes. In one example, the SPR is carried out at 25°C or 37°C in HBS-EP. HBS-EP is available from Teknova Inc (California; catalogue number H8022).

In an example, the affinity of the antibody or fragment is determined using SPR by

1. Coupling anti-mouse (or other relevant human, rat or non-human vertebrate antibody constant region species-matched) IgG (e.g., Biacore™ BR-1008-38) to a biosensor chip (e.g., GLM chip) such as by primary amine coupling;
2. Exposing the anti-mouse IgG (or other matched species antibody) to a test IgG antibody to capture test antibody on the chip;
3. Passing the test antigen over the chip's capture surface at 1024nM, 256nM, 64nM, 16nM, 4nM with a 0nM (i.e. buffer alone); and
4. And determining the affinity of binding of test antibody to test antigen using surface plasmon resonance, e.g., under an SPR condition discussed above (e.g., at 25°C in physiological buffer).

SPR can be carried out using any standard SPR apparatus, such as by Biacore™ or using the ProteOn XPR36™ (Bio-Rad®).

Regeneration of the capture surface can be carried out with 10mM glycine at pH1.7. This removes the captured antibody and allows the surface to be used for another interaction. The binding data can be fitted to 1:1 model inherent using standard techniques, e.g., using a model inherent to the ProteOn XPR36™ analysis software.

In another embodiment, the anti-OX40L antibodies described herein have a k_{ON} or "k_a" rate (e.g., as measured by SPR, e.g., at 37 °C) of approximately 400,000 to 3,000,000 M^{-1} s^{-1}, for example approximately 1,500,000 to 3,000,000 M^{-1} s^{-1} or approximately 2,000,000 to 3,000,000 M^{-1} s^{-1}. In another embodiment, optionally wherein the OX40L is human OX40L and/or optionally wherein the antibody is KY1005 the k_{ON} rate is approximately 1,900,000 M^{-1} s^{-1}, approximately 2,100,000 M^{-1} s^{-1}, approximately 2,200,000 M^{-1} s^{-1}, approximately 2,300,000 M^{-1} s^{-1} or approximately 2,500,000 M^{-1} s^{-1}. The k_{ON} rate may be approximately 2,200,000 M^{-1} s^{-1}. In another embodiment, optionally wherein the OX40L is rhesus OX40L and/or optionally wherein the antibody is KY1005, the k_{ON} rate is approximately 2,300,000 M^{-1} s^{-1}, approximately 2,500,000 M^{-1} s^{-1}, approximately 2,570,000 M^{-1} s^{-1}, approximately 2,600,000 M^{-1} s^{-1} or approximately 2,800,000 M^{-1} s^{-1}. The k_{ON} rate may be approximately 2,570,000 M^{-1} s^{-1}.

In another embodiment, the anti-OX40L antibodies described herein have a k_{OFF} or "k_d" rate (e.g., as measured by SPR, e.g., at 37 °C) of approximately 0.00100 to 0.00220 s^{-1}, for example approximately 0.00130 to 0.00210 s^{-1}, or approximately 0.00150 to 0.00200 s^{-1}. In another embodiment, optionally wherein the OX40L is human OX40L and/or optionally wherein the antibody is KY1005, the k_{OFF} rate is approximately 0.00150 to 0.00210 s^{-1}, or approximately 0.00160 to 0.00200 s^{-1}, e.g., approximately 0.00170 s^{-1}, approximately 0.00175 s^{-1}, approximately 0.00177 s^{-1}, approximately 0.00180 s^{-1} or approximately 0.00185 s^{-1}. The k_{OFF} rate may be approximately 0.00177 s^{-1}. In another embodiment, optionally wherein the OX40L is rhesus OX40L and/or optionally wherein the antibody is KY1005, the k_{OFF} rate is approximately 0.00180 to 0.00210 s^{-1}, is approximately 0.00185 s^{-1}, approximately 0.00192 s^{-1}, or approximately 0.00200 s^{-1}. The k_{OFF} rate may be approximately 0.00192 s^{-1}.

In another embodiment, the anti-OX40L antibodies described herein have a K_D (e.g., as measured by SPR, e.g., at 37 °C) of approximately 0.01 to 2.0 nM, for example approximately 0.3 to 1.5 nM, or approximately 0.5 to 1.1 nM. In another embodiment, optionally wherein the OX40L is human OX40L and/or optionally wherein the antibody is KY1005, the K_D is approximately 0.60 to 1.0 nM, or approximately 0.70 to 0.90 nM, e.g., approximately 0.75 nM, approximately 0.80 nM, approximately 0.81 nM, approximately 0.82 nM or approximately 0.87 nM. The K_D may be approximately 0.81 nM. In another embodiment, optionally wherein the OX40L is rhesus OX40L and/or optionally wherein the antibody is KY1005, the K_D is approximately 0.60 to 0.90 nM, is approximately 0.70 nM, approximately 0.75 nM, or approximately 0.80 nM. The K_D may be approximately 0.75 nM.

Sequences of antibodies 2D10 (also known as KY1005), 10A7 (also known as KY1007), 09H04 and 19H01 are disclosed herein. Sequences belonging to each antibody 2D10, 10A7, 09H04 and 19H01 are as identified in the sequence listing below. In some embodiments the sequences of antibodies are 2D10 and 10A7. Any list containing sequences from antibodies 2D10, 10A7, 09H04 and 19H01 may therefore be presented as a list of sequences from antibodies 2D10 and 10A7. In some embodiments, the sequences of antibody is 2D10. Any list containing sequences from antibodies 2D10, 10A7, 09H04 and 19H01 (or from antibodies 2D10 and 10A7) may therefore be presented as a list of sequences from antibody 2D10.

The antibody or fragment thereof may be a biosimilar of any antibody disclosed herein. The antibody or fragment thereof may be a biosimilar of 2D10. As used herein a "biosimilar" is a biological product that is highly similar to and has no clinically meaningful differences from a reference product. The reference product may be any antibody disclosed herein, such as 2D10. As used herein, whether a biological product is "highly similar" to a reference product may be determined using known techniques comparing product characteristics such as purity, chemical identity and bioactivity. The results from these comparative tests, along with other information, may be used to demonstrate that the biosimilar is highly similar to the reference product. Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. For example, these could include minor differences in the stabilizer or buffer compared to what is used in the reference product. In some instances, different glycosylation levels may be considered minor differences. Any differences between the proposed biosimilar product and the reference product are carefully evaluated by a regulator, such as the FDA to ensure the biosimilar meets the regulator's high approval standards. As mentioned above, slight differences (i.e., acceptable within-product variations) are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product. For both reference products and biosimilars, lot-to-lot differences (i.e., acceptable within-product differences) are carefully controlled and monitored. As used herein, whether a biological product has "no clinically meaningful differences" to a reference product means there are no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

The antibody or fragment thereof may specifically bind to human OX40L (hOX40L). The antibody may block or neutralise the interaction between hOX40L and hOX40 receptor. Methods for determining antagonism, neutralising or blocking functionality may be as described herein, or as well-known by those skilled in the art. For example, *in vitro* techniques include SPR and/or ELISA, which are described elsewhere herein.

The antibody or fragment thereof may specifically bind to hOX40L with a K_D of from 1 nM to 0.01 nM, optionally wherein the specific binding is measured by surface plasmon resonance (SPR).

The antibody or fragment thereof may compete for binding to hOX40L with 02D10.The antibody or fragment thereof may compete for binding to hOX40L with the antibody 02D10, wherein the antibody or fragment comprises a VH domain which comprises a HCDR3 comprising the motif VRGXYYY (SEQ ID NO: 235), wherein X is any amino acid. Optionally X is P or G.

In an embodiment, X is P or G. In an embodiment, X is selected from P, N, A or G. In another embodiment, X is selected from P, G or N. In another embodiment, X is selected from P, G or A.

In one embodiment, the antibody or fragment competes with the variable regions of 02D10 (e.g., competes with an antibody comprising the heavy chain variable region of SEQ ID No: 34 and the light chain variable region of SEQ ID No:48). In another embodiment, the antibody or fragment competes with 02D10 IgG4-PE having a heavy chain amino acid sequence of SEQ ID No:62 and a light chain amino acid sequence of SEQ ID No:64.

In one embodiment, the amino acid is any naturally-occurring amino acid.

The antibody or fragment thereof may antagonise specific binding of hOX40L to OX40, optionally as determined using SPR or ELISA. The antibody or fragment thereof may be referred to as an anti-OX40L antibody that antagonises OX40L accordingly.

The antibody or fragment thereof may decrease IL-2 secretion by at least 50% (e.g., 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-2 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay.

The antibody or fragment thereof may decrease IL-13 secretion by at least 50% (e.g., 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-13 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay.

The antibody may be a humanized, human or fully human antibody.

The fragment may be selected from the group consisting of multispecific antibodies (eg. bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies single-chain antibodies, single domain antibodies, domain antibodies, Fv fragments, $F(ab')_2$ fragments, dimeric variable regions (diabodies), linear antibodies, and epitope-binding fragments thereof.

The antibody or fragment thereof may comprise a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g., IGHJ6*02).

The antibody or fragment thereof may comprise a CDR selected from:

a. the HCDR3 of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46);
b. a CDR3 of any of the nanobodies having the variable region amino acid sequence of SEQ ID Nos: 177 to 213;

c. an HCDR3 of any of the antibodies having the variable region amino acid sequence of SEQ ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230; or

d. an HCDR3 of any of the antibodies having the variable region amino acid sequence of SEQ ID Nos: 232 or 234.

The antibody or fragment thereof may comprise the HCDR3 of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46).

The antibody or fragment thereof may comprise the HCDR2 of antibody 2D10 (SEQ ID No:38 or SEQ ID No:44).

The antibody or fragment thereof may comprise the HCDR1 of antibody 2D10 (SEQ ID No:36 or SEQ ID No:42).

The antibody or fragment thereof may comprise the LCDR3 of antibody 2D10 (SEQ ID No:54 or SEQ ID No:60).

The antibody or fragment thereof may comprise the LCDR2 of antibody 2D10 (SEQ ID No:52 or SEQ ID No:58).

The antibody or fragment thereof may comprise the LCDR1 of antibody 2D10 (SEQ ID No:50 or SEQ ID No:56).

The antibody or fragment thereof may comprise any one, two, three, four, five or six of the CDRs selected from the group consisting of:

the HCDR3 of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46),
the HCDR2 of antibody 2D10 (SEQ ID No:38 or SEQ ID No:44),
the HCDR1 of antibody 2D10 (SEQ ID No:36 or SEQ ID No:42),
the LCDR3 of antibody 2D10 (SEQ ID No:54 or SEQ ID No:60),
the LCDR2 of antibody 2D10 (SEQ ID No:52 or SEQ ID No:58) and
the LCDR1 of antibody 2D10 (SEQ ID No:50 or SEQ ID No:56).

The antibody or fragment thereof may comprise:

a. the CDRs of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);

b. the CDRs of any of the nanobodies having the variable region amino acid sequence of SEQ ID Nos: 177 to 213;

c. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of SEQ ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of SEQ ID Nos: 216, 218, 220, 222, 224, 226 or 228; or

d. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of SEQ ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of SEQ ID Nos:231 or 233.

The antibody or fragment thereof may comprise the CDRs of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3).

The antibody or fragment thereof may comprise the CDRH1 sequence of the VH region of 2D10 as in SEQ ID No: 34.

The antibody or fragment thereof may comprise the CDRH2 sequence of the VH region of 2D10 as in SEQ ID No: 34.

The antibody or fragment thereof may comprise the CDRH3 sequence of the VH region of 2D10 as in SEQ ID No: 34.

The antibody or fragment thereof may comprise the CDRL1 sequence of the VL region of 2D10 as in SEQ ID No: 48.

The antibody or fragment thereof may comprise the CDRL2 sequence of the VL region of 2D10 as in SEQ ID No: 48.

The antibody or fragment thereof may comprise the CDRL3 sequence of the VL region of 2D10 as in SEQ ID No: 48.

The antibody or fragment thereof may comprise any one, two, three, four, five or six of the CDRs selected from the group consisting of:

the CDRH1 sequence of the VH region of 2D10 as in SEQ ID No: 34,
the CDRH2 sequence of the VH region of 2D10 as in SEQ ID No: 34,
the CDRH3 sequence of the VH region of 2D10 as in SEQ ID No: 34,
the CDRL1 sequence of the VL region of 2D10 as in SEQ ID No: 48,
the CDRL2 sequence of the VL region of 2D10 as in SEQ ID No: 48 and
the CDRL3 sequence of the VL region of 2D10 as in SEQ ID No: 48.

The antibody or fragment thereof may comprise an IgG4 constant region. The IgG4 constant region may be IgG4*1, IgG4*2, IgG4*3 or IgG4-PE. The IgG4 may have an amino acid sequence according to any one of SEQ ID Nos: 121,123, 125, 127, 129 or 131.

The antibody or fragment thereof may comprise an IgG4 constant region comprising a Leu235Glu mutation and/or a Ser228Pro mutation. Ser228Pro / Leu235Glu mutations are according to the EU index numbering system.

The antibody or fragment thereof may comprise an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128.

The antibody or fragment thereof may comprise an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128; a VH domain having an amino acid sequence according to SEQ ID No:34 and a VL domain having an amino acid sequence according to SEQ ID No:48.

The antibody or fragment thereof may comprise an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128 and a VH and/or VL domain of an anti-OX40L antibody disclosed herein.

The antibody or fragment thereof may comprise an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128 and a VH and/or VL domain comprising CDR sequences of an anti-OX40L antibody disclosed herein. The antibody or fragment thereof may comprise an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128 and

a. the CDRs of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3);
b. the CDRs of any of the nanobodies having the variable region amino acid sequence of SEQ ID Nos: 177 to 213;
c. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of SEQ ID Nos: 215, 217, 219, 221, 223, 225, 227, 229 or 230, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of SEQ ID Nos: 216, 218, 220, 222, 224, 226 or 228; or
d. the heavy chain CDRs of any of the antibodies having the heavy chain variable region amino acid sequence of SEQ ID Nos: 232 or 234, and the light chain CDRs of any of the antibodies having the light chain variable region amino acid sequence of SEQ ID Nos:231 or 233.

The antibody or fragment thereof may comprise an IgG4-PE constant region having a heavy chain having an amino acid sequence according to SEQ ID No:62 and a light chain having an amino acid sequence according to SEQ ID No:64.

The antibody may be oxelumab.

Embodiments

In the following embodiments, the antibody may be 02D10.

The antibody or fragment thereof may be administered at most once every 12 weeks. The antibody or fragment thereof may be administered every 12 weeks to 24 weeks. The antibody or fragment thereof may be administered every 12 weeks or every 24 weeks. The administration may be by subcutaneous injection.

The dose may be 125 mg. The dose may be an initial dose of 250 mg followed by 125 mg. The administration may be by subcutaneous injection.

The dose may be 125 mg administered every 12 weeks. The administration may be by subcutaneous injection.

The dose may be an initial dose of 250 mg followed by 125 mg administered every 12 weeks. The administration may be by subcutaneous injection.

Advantages include 02D10 (also referred to as KY1005 or Amlitelimab) as a potential first-in-class anti-OX40-L. Subcutaneous administration is advantageously convenient. Furthermore, as shown herein ~70% of IGA 0/1 patients with sustained response off drug for 24 weeks. 02D10 also provides an attractive target product profile due to infrequent dosing regimen and durability of response, addressing mixed-phenotype AD populations.

In some embodiments, the method defined herein may further comprise the use of a biomarker described herein. The use of a biomarker may for instance be any use defined herein. The biomarker may be any one or more biomarker described herein. The biomarker may be selected from the group consisting of IL-13, IL-22, and IL-17A. IL-13 may be considered a Th2 biomarker. IL-22 and IL-17A may be considered non-Th2 biomarkers. The effect of 02D10 (also referred to as KY1005 or Amlitelimab) on IL-13, IL-22, and IL-17A disclosed herein indicates that in some embodiments, the methods may be effective in both Th2 and non-Th2 AD patient populations.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Diagnostic biomarkers

The method may comprise use of a diagnostic biomarker. The diagnostic biomarker may be selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. Any mention of a "biomarker" in the following paragraphs under the heading of "Diagnostic biomarkers" may refer to a diagnostic biomarker.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in treating AD in a patient with a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in the treatment of AD in a patient population classified as Th2 high. Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in the treatment of AD in a patient population classified as Th2 low.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in treating Th2 high AD.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in treating Th2 low AD.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in treating Th2 high and Th2 low AD.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in treating AD patients with mixed inflammatory responses.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in the treatment of AD in a patient having an elevated level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for therapeutic use in inflammatory diseases with AD-associated biomarkers.

Some embodiments include a pharmaceutical composition comprising an OX40L blocking agent for the uses as described herein.

The biomarker may be selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. IL-13 may be considered a Th2 biomarker. Patients with an elevated IL-13 level may be classified as a Th2 AD patient or Th2 high AD patient. The method may comprise detecting an elevated IL-13 level and classifying the patient as a Th2 AD patient or Th2 high AD patient. IL-22 and IL-17A may be considered non-Th2 biomarkers. Patients with an elevated IL-22 and/or IL-17A level may be classified as a non-Th2 AD patient or Th2 low AD patient. The method may comprise detecting an elevated IL-22 and/or IL-17A level and classifying the patient as a non-Th2 AD patient or Th2 low AD patient. In some embodiments, the effect of 02D10 (also referred to as KY1005 or Amlitelimab) on IL-13, IL-22, and IL-17A disclosed herein indicates that the methods may be effective in both Th2 and non-Th2 AD patient populations. The subject may be classified as a Th2 AD patient and/or a non-Th2 AD patient. The subject may be classified as a Th2 high AD patient and/or a Th2 low AD patient. The subject may be a Th2 AD patient. The subject may be a non-Th2 AD patient. The subject may be a Th2 high AD. The patient may be a Th2 low AD patient.

According to certain aspects, methods for treating AD are provided which comprise: (a) selecting a subject who exhibits a level of at least one AD-associated biomarker prior to or at the time of treatment which signifies the disease state; and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof. In certain embodiments, the patient is selected by determining if the level of an AD-associated biomarker is elevated. The level of an AD-associated biomarker is determined or

quantified by acquiring a sample from the patient for a biomarker assay known in the art. In certain other embodiments, a patient is selected by determining the patient has an elevated level of an AD-associated biomarker from the patient. In certain embodiments of this aspect, the subject is selected on the basis of an elevated level of IL-13, IL-22 and/or IL-17A.

The patient sample may be a blood, serum, tissue biopsy or other sample. The patient sample may be acquired at any point before, after, or during a course of treatment.

Some embodiments also include methods for determining whether a subject is a suitable subject for whom administration of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, would be beneficial. For example, if an individual, prior to receiving a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, exhibits a level of an AD-associated biomarker which signifies the disease state, the individual is therefore identified as a suitable patient for whom administration of a pharmaceutical composition of (e.g., a composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof) would be beneficial. In a related embodiment, includes methods for treating suitable subjects, wherein a suitable subject may be more susceptible to AD, for example, due to race or ethnicity. Some embodiments include methods comprising administering an anti-OX40L antibody, or antigen-binding fragment thereof, to African-American subjects who may be more susceptible to AD. Such a subject population may have an elevated level of an AD-associated biomarker.

According to certain exemplary embodiments, an individual may be identified as a suitable subject for anti-OX40L antibody, or antigen-binding fragment thereof therapy, if the individual exhibits an elevated level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

According to other exemplary embodiments, the present invention provides methods for treating AD in a subject, the methods comprising: (a) selecting a subject who exhibits an elevated level of at least one AD-associated biomarker; and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof. Exemplary AD-associated biomarkers that can be evaluated and/or measured in the context of the present invention include IL-13, IL-22, IL-17A, IL-31 and IgE. In some embodiments, the methods comprise determining the level of an AD-associated biomarker in a patient in need thereof, selecting a patient with an elevated level of the AD-associated biomarker, and administering a therapeutically effective amount anti-OX40L antibody, or antigen-binding fragment thereof. In some embodiments, the patient is selected by determining the patient has level of an AD-associated biomarker in a patient. In some embodiments, the level of an AD-associated biomarker is determined by an assay or test known in the art or as disclosed elsewhere herein. In one embodiment, the patient is selected on the basis of exhibiting an elevated level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE, prior to or at the time of treatment. In one embodiment, the patient is selected on the basis of exhibiting an elevated level of one or more

biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE prior to or at the time of treatment.

In certain embodiments, the methods may be used to treat patients that show elevated levels of one or more AD-associated biomarkers (described elsewhere herein). For example, the methods of the present invention comprise administering an anti-OX40L antibody, or antigen-binding fragment thereof, to patients with elevated levels of biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. In some embodiments, the methods herein may be used to treat AD in children who are < 1 year old.

According to certain aspects , methods for treating AD are provided which comprise: (a) selecting a subject who exhibits a level of at least one AD-associated biomarker prior to or at the time of treatment which signifies the disease state; and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof. In certain embodiments of this aspect, the subject is selected on the basis of an elevated level of biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

Some embodiments also include methods for determining whether a subject is a suitable subject for whom administration of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, would be beneficial. For example, if an individual, prior to receiving a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, exhibits a level of an AD-associated biomarker which signifies the disease state, the individual is therefore identified as a suitable patient for whom administration of a pharmaceutical composition (e.g., a composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof) would be beneficial.

As used herein, the expression "a suitable subject" means a human or non-human mammal that exhibits one or more symptoms or indications of AD, and/or who has been diagnosed with AD. A suitable subject may have been assigned a disease severity by any suitable method disclosed herein. In certain embodiments, the methods may be used to treat patients that show elevated levels of one or more AD-associated biomarkers (described elsewhere herein). Some embodiments comprise administering an anti-OX40L antibody, or antigen-binding fragment thereof, to patients with elevated levels of biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. The term "a suitable subject" may also include, e.g., subjects who, prior to treatment, exhibit (or have exhibited) one or more indications of AD.

In some embodiments,, "a suitable subject" may include a subset of population which is more susceptible to AD or may show an elevated level of an AD-associated biomarker such as IL-13, IL-22, IL-17A, IL-31 and IgE.

According to certain exemplary embodiments, an individual may be identified as a suitable subject for treatment with an anti-OX40L antibody, or antigen-binding fragment thereof, if the

individual exhibits an elevated level of one or more biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

Some embodiments also include methods for determining whether a subject is a suitable subject for whom administration of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof would be beneficial. For example, if an individual, prior to receiving a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, exhibits a level of an AD-associated biomarker which signifies the disease state, the individual is therefore identified as a suitable patient for whom administration of a pharmaceutical composition (e.g., a composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof) would be beneficial. According to certain exemplary embodiments, an individual may be identified as a good candidate for therapy comprising administration of an anti-OX40L antibody, or antigen-binding fragment thereof, if the individual exhibits an elevated level of one or more biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

According to certain exemplary embodiments, are methods for treating AD in a subject, the methods comprising: (a) selecting a subject who exhibits an elevated level of at least one AD-associated biomarker; and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof. According to a related aspect, methods for treating AD are provided which comprise administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker in the subject. Exemplary AD-associated biomarkers that can be evaluated and/or measured include: IL-13, IL-22, IL-17A, IL-31 and IgE.

In some embodiments, an anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method for treating AD in a subject, wherein the subject exhibits an elevated level of at least one AD-associated biomarker prior to or at the time of treatment.

According to certain embodiments, is provided methods for treating AD in a subject comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the subject has been diagnosed with AD and has also been selected for treatment on the basis of the subject exhibiting an increased level of an AD-associated biomarker before treatment. The increased level may be increased as compared to a reference level of the biomarker. The reference level of the biomarker may be the normal level in a healthy subject. The reference level may be a normal level for the subject, which may be determined for example by comparison to a level of the biomarker when the subject was healthy, for example using samples obtained from the subject before the onset of AD. The reference level may be expression of the biomarker in a subset of subjects diagnosed with AD and/or expression of the biomarker in healthy subjects.

According to certain aspects, methods for treating AD are provided which comprise: (a) selecting a subject who exhibits a level of at least one AD-associated biomarker prior to or at the time of treatment which signifies the disease state, and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof. In certain embodiments of this aspect, the subject is selected on the basis of an elevated level of biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

In some embodiments, an anti-OX40L antibody, or antigen-binding fragment thereof for use in treating AD in a patient, wherein the treatment comprises assaying a sample from a patient to determine if a patient has a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE; and administering a therapeutically effective amount of the anti-OX40L antibody, or antigen-binding fragment thereof if IL-13, IL-22, IL-17A, IL-31 and IgE is present.

In one aspect, is provided a method of determining whether a patient suspected to suffer from AD is a candidate for therapy comprising administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for the said AD comprising the step of subjecting a patient's biological sample to at least one assay to measure at baseline the level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE, wherein when the biological sample of the biomarker level is high relative to a reference level of expression of the biomarker, the patient is identified as a candidate for therapy comprising administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for AD. In some embodiments the at least one assay is an Olink assay. In some embodiments the at least one assay is a Simoa assay.

In some embodiments is a method for treating AD in a patient in need thereof, wherein the method comprises (a) measuring the level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE in the biologic fluid of the patient; (b) comparing the measured level with a reference level or threshold level; and (c) if the level of said biomarker is above the reference level or threshold level, administering to the patient an anti-OX40L antibody, or antigen-binding fragment thereof.

In some embodiments is a method for treating a patient with AD with an anti-OX40L antibody, or antigen-binding fragment thereof, comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, to the patient, wherein the level of a biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE, in the patient's biological sample is high relative to a reference level of expression of the biomarker.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Monitoring biomarkers

The method may comprise use of a monitoring biomarker. The monitoring biomarker may be selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. Any mention of a "biomarker" in the following paragraphs under the heading of "Monitoring biomarkers" may refer to a monitoring biomarker. Uses of monitoring biomarkers described in the following paragraphs under the heading of "Monitoring biomarkers" may alternatively be described as uses of pharmacodynamic or response biomarkers as appropriate.

Some embodiments also provide methods for decreasing the level of one or more AD-associated biomarker(s) in a subject, or improving one or more AD-associated parameter(s) in a subject, wherein the methods comprise sequentially administering to a subject in need thereof a single initial dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, followed by one or more secondary doses of the pharmaceutical composition comprising the anti-OX40L antibody, or antigen-binding fragment thereof. The single initial dose may be any dose defined herein. The single initial dose may be a loading dose defined herein. The one or more secondary doses may be any doses defined herein. The one or more secondary doses may be a maintenance dose defined herein. Any reference to the term "dose" under the heading of "Monitoring biomarkers" may refer instead to an "injection".

According to certain embodiments, isprovided methods for decreasing the level of one or more AD-associated biomarker(s) in a subject, or improving one or more AD-associated parameter(s) in a subject, wherein the methods comprise administering to the subject a dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

According to a related aspect, methods for treating AD are provided which comprise administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker (for example IL-13, IL-22, IL-17A, IL-31 and IgE). The decrease may be by day 1, 29, 113, 169, 253 or later in the subject following administration. The decrease may be measured in a sample obtained from the subject on day 1, 29, 113, 169, 253 or later in the subject following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease in IL-13, IL-22, IL-17A, IL-31 and IgE level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.05 $\log_{10}$ to a -0.30 $\log_{10}$ decrease, such as about a -0.1 $\log_{10}$ decrease or about a -0.15 $\log_{10}$ decrease in IL-13 level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.05 $\log_{10}$ to a -0.30 $\log_{10}$ decrease, such as about a -0.1 $\log_{10}$ decrease or about a -0.15 $\log_{10}$ decrease in IL-22 level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.01 $\log_{10}$ to a -0.20 $\log_{10}$

decrease, such as about a -0.02 log_{10} decrease or about a -0.025 log_{10} decrease in IL-17A level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 log_{10} to a -1.0 log_{10} decrease in IL-13, IL-22, and/or IL-17A level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 log_{10} to a -1.0 log_{10} decrease, such as a -0.3 log_{10} to a -0.6 log_{10} decrease, such as about a -0.4 log_{10} decrease or about a -0.45 log_{10} decrease in IL-13 level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 log_{10} to a -1.0 log_{10} decrease, such as a -0.40 log_{10} to a -0.70 log_{10} decrease, such as about a -0.5 log_{10} decrease or about a -0.55 log_{10} decrease in IL-22 level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 log_{10} to a -1.0 log_{10} decrease, such as a -0.01 log_{10} to a -0.10 log_{10} decrease, such as about a -0.05 log_{10} decrease or about a -0.055 log_{10} decrease in IL-17A level from the baseline at day 113 or later following administration. Alternatively, administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker by day 4, 8, 15, 22, 25, 29, 36 or later in the subject following administration. In certain embodiments, the patient exhibits between 5% and 20% decrease in IL-13, IL-22, IL-17A, IL-31 and IgE level from the baseline at day 36 or later following administration.

In another aspect, is provided monitoring the effectiveness of treatment of moderate-to-severe AD in a subject with an anti-OX40L antibody, or antigen-binding fragment thereof, the method comprising: (a) determining the expression level of an AD-associated biomarker, such as IL-13, IL-22, IL-17A, IL-31 and IgE in a biological sample acquired from the subject before treatment with the anti-OX40L antibody, or antigen-binding fragment thereof; (b) determining the expression level of at least one of IL-13, IL-22, IL-17A, IL-31 and IgE in a biological sample acquired from the subject after treatment with the anti-OX40L antibody, or antigen-binding fragment thereof; (c) comparing the level determined in step (a) with the level in step (b); and (d) concluding that the treatment is effective when the level determined in step (b) is lower than the level determined in step (a), or concluding that the treatment is not effective when the level determined in step (b) is the same or higher than the level determined in step (a). In one embodiment, the level in step (b) is determined after determining the level in step (a). In one embodiment, the biomarker is one or more of the biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE and if IL-13, IL-22, IL-17A, IL-31 and IgE levels decrease following administration of the anti-OX40L antibody, or antigen-binding fragment thereof, then treatment with the anti-OX40L antibody, or antigen-binding fragment thereof is determined to be effective.

The expression level of the biomarker can be determined after administration of the anti-OX40L antibody, or antigen-binding fragment thereof, and compared to the expression level prior to administration of the anti-OX40L antibody, or antigen-binding fragment thereof. The dose or the dosing regimen of the anti-OX40L antibody, or antigen-binding fragment thereof can be adjusted

following the determination. For example, if the expression of the biomarker fails to decrease following administration of the anti-OX40L antibody, or antigen-binding fragment thereof, then treatment with the anti-OX40L antibody, or antigen-binding fragment thereof can be stopped, or the dose of the anti-OX40L antibody, or antigen-binding fragment thereof can be increased. If expression of the biomarker decreases following administration of the antagonist, the dosage of the antagonist can be maintained or decreased, such as to identify a minimal effective dose. In some embodiments, treatment is maintained at the minimal effective dose.

In another aspect, is provided methods for monitoring a subject's response to treatment with an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the subject has moderate-to-severe AD, the method comprising: (a) determining the expression level of at least one of IL-13, IL-22, IL-17A, IL-31 and IgE in a biological sample from the subject following administration of the anti-OX40L antibody, or antigen-binding fragment thereof, to the subject; and (b) providing an indication that the treatment should be continued if the expression level of IL-13, IL-22, IL-17A, IL-31 and IgE has decreased as compared to the level before treatment with the anti-OX40L antibody. In one embodiment, the biomarker is one or more of the biomarkers selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE and if IL-13, IL-22, IL-17A, IL-31 and IgE levels are determined to decrease following administration of the anti-OX40L antibody, or antigen-binding fragment thereof, then an indication is provided to continue treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

As will be appreciated by a person of ordinary skill in the art, an increase or decrease in an AD-associated biomarker can be determined by comparing (i) the level of the biomarker measured in a subject at a defined time point after administration of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof to (ii) the level of the biomarker measured in the patient prior to the administration of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof (i.e., the "baseline measurement"). The defined time point at which the biomarker is measured can be, e.g., at about 4 hours, 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 15 days, 20 days, 35 days, 40 days, 50 days, 55 days, 60 days, 65 days, 70 days, 75 days, 80 days, 85 days, or more after administration of the of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof. The defined time point at which the biomarker is measured can be, e.g., day 1, 29, 113, 169, 253 or later after administration of the of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, a subject may exhibit a decrease in the level of one or more of IL-13, IL-22, IL-17A, IL-31 and IgE following administration of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof. For example, at about day 1, 29, 113, 169, 253 or later, following administration of a dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, the subject, , may exhibit a

decrease in one or more of IL-13, IL-22, IL-17A, IL-31 and IgE of about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more from baseline (wherein "baseline" is defined as the level of IL-13, IL-22, and/or IL-17A in the subject just prior to the first administration). For example, at about day 1, day 4, day 8, day 15, day 22, day 25, day 29, day 36, day 43, day 50, day 57, day 64, day 71 or day 85, following administration of a dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, the subject, according to the present invention, may exhibit a decrease in one or more of IL-13, IL-22, IL-17A, IL-31 and IgE of about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more from baseline (wherein "baseline" is defined as the level of IL-13, IL-22, IL-17A, IL-31 and IgE in the subject just prior to the first administration).

Some embodiments also provide methods for treating AD by administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the subject has been diagnosed with AD, has already been treated with the anti-OX40L antibody, or antigen-binding fragment thereof for a defined period of time, and has been selected for further treatment with the anti-OX40L antibody, or antigen-binding fragment thereof on the basis of exhibiting reduced expression of a biomarker (e.g., IL-13, IL-22, IL-17A, IL-31 and IgE) after treatment for the defined period of time (e.g., 1 day, 29 days, 113 days, 169 days, 253 days), wherein the reduced expression of the biomarker is determined based on a comparison to the level of expression of the respective biomarker in the subject prior to treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

Some embodiments also include an anti-OX40L antibody, or antigen-binding fragment thereof for use in a method for treating AD in a subject, wherein the subject exhibits a higher level of at least one AD-associated biomarker prior to or at the time of treatment (e.g., as compared to a population of AD patients or a subset of the AD patient population), as compared to a reference level of the biomarker. Some embodiments also include an anti-OX40L antibody, or antigen-binding fragment thereof for use in a method for treating AD in a subject, wherein the subject exhibits a lower level of at least one AD-associated biomarker after treatment with the anti-OX40L antibody, or antigen-binding fragment thereof for a defined period of time (e.g., 1 day, 29 days, 113 days, 169 days, 253 days) as compared to the level of the one or more biomarkers prior to treatment.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.

Pharmacodynamic/response biomarkers

The method may comprise use of a pharmacodynamic biomarker or response biomarker. The pharmacodynamic biomarker or response biomarker may be selected from the group consisting of IL-

13, IL-22, IL-17A, IL-31 and IgE. Any mention of a "biomarker" in the following paragraphs under the heading of "Pharmacodynamic/response biomarkers" may refer to either a pharmacodynamic biomarker or a response biomarker. Uses of monitoring biomarkers described in the following paragraphs under the heading of "Pharmacodynamic/response biomarkers" may alternatively be described as uses of monitoring biomarkers as appropriate.

Some embodiments provide an *in vitro* method for determining efficacy of a treatment of a subject having AD by administration of an anti-OX40L antibody, or antigen-binding fragment thereof, comprising determining *in vitro* a level of one or more biomarker selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE in a sample of said subject having AD, wherein said treatment is considered efficient if the level of IL-13, IL-22 and/or IL-17A is decreased. The decrease may be a decrease in the level of IL-13, IL-22, IL-17A, IL-31 and IgE by day 1, 29, 113, 169, 253 or later in the subject following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease in IL-13, IL-22, IL-17A, IL-31 and IgE level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.05 $\log_{10}$ to a -0.30 $\log_{10}$ decrease, such as about a -0.1 $\log_{10}$ decrease or about a -0.15 $\log_{10}$ decrease in IL-13 level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.05 $\log_{10}$ to a -0.30 $\log_{10}$ decrease, such as about a -0.1 $\log_{10}$ decrease or about a -0.15 $\log_{10}$ decrease in IL-22 level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -0.50 $\log_{10}$ decrease, such as a -0.01 $\log_{10}$ to a -0.20 $\log_{10}$ decrease, such as about a -0.02 $\log_{10}$ decrease or about a -0.025 $\log_{10}$ decrease in IL-17A level from the baseline at day 29 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -1.0 $\log_{10}$ decrease in IL-13, IL-22, and/or IL-17A level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -1.0 $\log_{10}$ decrease, such as a -0.3 $\log_{10}$ to a -0.6 $\log_{10}$ decrease, such as about a -0.4 $\log_{10}$ decrease or about a -0.45 $\log_{10}$ decrease in IL-13 level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -1.0 $\log_{10}$ decrease, such as a -0.40 $\log_{10}$ to a -0.70 $\log_{10}$ decrease, such as about a -0.5 $\log_{10}$ decrease or about a -0.55 $\log_{10}$ decrease in IL-22 level from the baseline at day 113 or later following administration. In certain embodiments, the patient exhibits between a -0.01 $\log_{10}$ to a -1.0 $\log_{10}$ decrease, such as a -0.01 $\log_{10}$ to a -0.10 $\log_{10}$ decrease, such as about a -0.05 $\log_{10}$ decrease or about a -0.055 $\log_{10}$ decrease in IL-17A level from the baseline at day 113 or later following administration. Alternatively, administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker by day 4, 8, 15, 22, 25, 29, 36 or later in the subject following administration. In certain embodiments, the patient exhibits between 5% and 20% decrease in IL-13, IL-22, IL-17A, IL-31 and IgE level from the baseline at day 36 or later following administration.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof for use in improving an AD-associated parameter, or for reducing the level of one or more AD-associated biomarkers in a subject in need thereof, wherein the pharmaceutical composition is sequentially administered to the subject as a single initial dose followed by one or more secondary doses. The one or more AD-associated biomarkers may be selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE. The single initial dose may be any dose defined herein. The single initial dose may be a loading dose defined herein. The one or more secondary doses may be any doses defined herein. The one or more secondary doses may be a maintenance dose defined herein. Any reference to the term "dose" under the heading of "Pharmacodynamic/response biomarkers" may refer instead to an "injection".

In addition, some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in reducing the level of one or more AD-associated biomarkers in a subject in need thereof. The one or more AD-associated biomarkers may be selected from the group consisting of IL-13, IL-22, IL-17A, IL-31 and IgE.

Some embodiments include a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for use in the treatment of AD in a subject wherein the treatment results in a decrease in one or more AD-associated biomarkers in the subject (for example, by day 1, 29, 113, 169, or 253) following treatment as compared to the level of biomarker in the subject prior to treatment. In certain embodiments, the AD-associated biomarker is at least one of IL-13, IL-22, IL-17A, IL-31 and IgE.

According to other aspects of, methods for treating AD are provided which comprise administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker (e.g., IL-13, IL-22, IL-17A, IL-31 and IgE) at a time after administration of the pharmaceutical composition, as compared to the level of the biomarker in the subject prior to the administration.

As will be appreciated by a person of ordinary skill in the art, an increase or decrease in an AD-associated biomarker can be determined by comparing (i) the level of the biomarker measured in a subject at a defined time point after administration of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof to (ii) the level of the biomarker measured in the patient prior to the administration of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof (i.e., the "baseline measurement"). The defined time point at which the biomarker is measured can be, e.g., at about 4 hours, 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 15 days, 20 days, 35 days, 40 days, 50 days, 55 days, 60 days, 65 days, 70 days, 75 days, 80 days, 85 days, or more after administration of the of the pharmaceutical composition comprising an anti-OX40L

antibody, or antigen-binding fragment thereof. The defined time point at which the biomarker is measured can be, e.g., day 1, 29, 113, 169, 253 or later after administration of the of the pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof. According to certain particular embodiments, a subject may exhibit a decrease in the level of one or more of IL-13, IL-22, IL-17A, IL-31 and IgE following administration of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof. For example, following administration of a dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, the subject, may exhibit a decrease in IL-13, IL-22, IL-17A, IL-31 and IgE of about 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more from baseline (wherein "baseline" is defined as the level of IL-13, IL-22, IL-17A, IL-31 and IgE in the subject just prior to the first administration).

According to other aspects , methods for treating AD are provided which comprise administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker (e.g., IL-13, IL-22, IL-17A, IL-31 and IgE) at a time after administration of the pharmaceutical composition, as compared to the level of the biomarker in the subject prior to the administration.

In other aspects provide methods for decreasing the level of one or more AD-associated biomarker(s) in a subject, or improving one or more AD-associated parameter(s) in a subject, wherein the methods comprise sequentially administering to a subject in need thereof a single initial dose of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, followed by one or more secondary doses of the pharmaceutical composition comprising the anti-OX40L antibody, or antigen-binding fragment thereof.

According to certain embodiments, is provided methods for decreasing the level of one or more AD-associated biomarker(s) in a subject, or improving one or more AD-associated parameter(s) in a subject, wherein the methods comprise administering to the subject a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

In further configurations, there are provided the above-mentioned embodiments comprising administering a therapeutically effective amount of an OX40L antagonist antibody or antigen-binding fragment thereof.Listed below are further embodiments.

EMBODIMENTS

1. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

2. A method according to embodiment 1, wherein the antibody or fragment thereof is administered via subcutaneous injection.

3. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof.

4. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug.

5. The method of embodiment 4 wherein after administering the disease modifying drug, the subject achieves an IGA-AD score of 0 or 1 for at least six months.

6. The method of any one of embodiments 4 or 5 wherein after treatment with the disease modifying drug is stopped, the subject maintains an IGA-AD score of 0 or 1 for at least six months.

7. The method of any one of embodiments 5 or 6 wherein the at least six months is at least seven months, at least eight months or at least nine months.

8. The method of any one of embodiments 4 to 7 wherein a therapeutic effect persists after the last administration of the antibody or fragment thereof by at least around six half lives of the antibody or fragment thereof.

9. The method of embodiment 8 wherein the at least six half lives is at least around seven half lives, at least around eight half lives or at least around nine half lives of the antibody or fragment thereof.

10. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof,

optionally according to any one of embodiments 1 to 9, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 2 to 6 months.

11. The method of embodiment 10 wherein the antibody or fragment thereof is administered at least twice with at least one interval of 2 to 5.5 months, at least one interval of 2 to 5 months, at least one interval of 2 to 4.5 months, or at least one interval of 2 to 4 months.

12. The method of any one of embodiments 10 or 11 wherein the antibody or fragment thereof is administered at least twice with at least one interval of around 3 months.

13. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 12, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 6 months.

14. The method of embodiment 13 wherein the antibody or fragment thereof is administered at least twice with at least one interval of 5.5 months, at least one interval of 5 months, at least one interval of 4.5 months, or at least one interval of 4 months.

15. The method of any one of embodiments 13 or 14 wherein the antibody or fragment thereof is administered at least twice with at least one interval of around 3 months.

16. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 15, wherein a post-administration EASI score is reduced at least 10% relative to a baseline EASI score.

17. The method of embodiment 16 wherein the post-administration EASI score is reduced at least 10% relative to the baseline EASI score on day 15 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

18. The method of any one of embodiments 16 to 17 wherein the post-administration EASI score is reduced at least 15% relative to the baseline EASI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

19. The method of any one of embodiments 16 to 18 wherein the post-administration EASI score is reduced at least 20% or at least 30% relative to the baseline EASI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

20. The method of any one of embodiments 16 to 19 wherein the post-administration EASI score is reduced at least 40% or at least 45% relative to the baseline EASI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

21. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 20, wherein a post-administration vIGA-AD score is reduced at least 10% relative to a baseline vIGA-AD score.

22. The method of embodiment 21 wherein the post-administration vIGA-AD score is reduced at least 10% relative to the baseline vIGA-AD score on day 15 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

23. The method of any one of embodiments 21 or 22 wherein the post-administration vIGA-AD score is reduced at least 15% relative to the baseline vIGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

24. The method of any one of embodiments 21 to 23 wherein the post-administration vIGA-AD score is reduced at least 20% or at least 30% relative to the baseline vIGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

25. The method of any one of embodiments 21 to 24 wherein the post-administration vIGA-AD score is reduced at least 40% or at least 45% relative to the baseline vIGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

26. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 25, wherein a post-administration IGA-AD score is reduced at least 10% relative to a baseline IGA-AD score.

27. The method of embodiment 26 wherein the post-administration IGA-AD score is reduced at least 10% relative to the baseline IGA-AD score on day 15 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

28. The method of any one of embodiments 26 to 27 wherein the post-administration IGA-AD score is reduced at least 15% relative to the baseline IGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

29. The method of any one of embodiments 26 to 28 wherein the post-administration IGA-AD score is reduced at least 20% or at least 30% relative to the baseline IGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

30. The method of any one of embodiments 26 to 29 wherein the post-administration IGA-AD score is reduced at least 40% or at least 45% relative to the baseline IGA-AD score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

31. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 30, wherein a post-administration BSA score is reduced at least 10% relative to a baseline BSA score.

32. The method of embodiment 31 wherein the post-administration BSA score is reduced at least 10% relative to the baseline BSA score on day 29 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

33. The method of any one of embodiments 31 to 32 wherein the post-administration BSA score is reduced at least 20% relative to the baseline BSA score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

34. The method of any one of embodiments 31 to 33 wherein the post-administration BSA score is reduced at least 30% or at least 35% relative to the baseline BSA score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

35. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof,

optionally according to any one of embodiments 1 to 34, wherein a post-administration SCORAD index is reduced at least 10% relative to a baseline SCORAD index.

36. The method of embodiment 35 wherein the post-administration SCORAD index is reduced at least 10% relative to the baseline SCORAD index on day 29 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

37. The method of any one of embodiments 35 to 36 wherein the post-administration SCORAD index is reduced at least 20% relative to the baseline SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

38. The method of any one of embodiments 35 to 37 wherein the post-administration SCORAD index is reduced at least 30% or at least 35% relative to the baseline SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

39. The method of any one of embodiments 35 to 38 wherein the post-administration SCORAD index is reduced at least 45% or at least 60% relative to the baseline SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

40. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 39, wherein a post-administration PO-SCORAD index is reduced at least 10% relative to a baseline PO-SCORAD index.

41. The method of embodiment 40 wherein the post-administration PO-SCORAD index is reduced at least 10% relative to the baseline PO-SCORAD index on day 29 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

42. The method of any one of embodiments 40 to 41 wherein the post-administration PO-SCORAD index is reduced at least 15% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

43. The method of any one of embodiments 40 to 42 wherein the post-administration PO-SCORAD index is reduced at least 20% or at least 30% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

44. The method of any one of embodiments 40 to 43 wherein the post-administration PO-SCORAD index is reduced at least 40% or at least 50% relative to the baseline PO-SCORAD index on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

45. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 44, wherein a post-administration DQLI score is reduced at least 10% relative to a baseline DQLI score.

46. The method of embodiment 45 wherein the post-administration DQLI score is reduced at least 10% relative to the baseline DQLI score on day 85 through at least day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

47. The method of any one of embodiments 45 to 46 wherein the post-administration DQLI score is reduced at least 20% relative to the baseline DQLI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

48. The method of any one of embodiments 45 to 47 wherein the post-administration DQLI score is reduced at least 30% or at least 35% relative to the baseline DQLI score on around day 113 after administration of the anti-OX40L antibody, or antigen-binding fragment thereof.

49. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of embodiments 1 to 48, wherein the subject is a chronic Atopic Dermatitis patient.

50. A method according to any preceding embodiment wherein the dose is of from 20 mg to 1000 mg.

51. A method according to any preceding embodiment wherein the dose is of from 20 mg to 600 mg.

52. A method according to any preceding embodiment wherein the dose is up to 550 mg, up to 500 mg, up to 450 mg, up to 400 mg, up to 350 mg, up to 300 mg, up to 250 mg, up to 200 mg, up to 150 mg, up to 120 mg, up to 100 mg, or up to 50 mg.

53. A method according to any preceding embodiment wherein the dose is up to 500 mg, up to 250 mg, or up to 150 mg.

54. A method according to any preceding embodiment wherein the dose is at least 50 mg, at least 100 mg, at least 120 mg, at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg, at least 350 mg, at least 400 mg, at least 450 mg, at least 500 mg or at least 550 mg.

55. A method according to any preceding embodiment wherein the dose is at least 50 mg, at least 120 mg or at least 150 mg.

56. A method according to any preceding embodiment wherein the dose is selected from the group consisting of from 25 mg to 500 mg; from 50 mg to 450 mg; from 100 mg to 350 mg; from 120 mg to 300 mg; from 150 mg to 250 mg; and from 200 mg to 250 mg.

57. A method according to any preceding embodiment wherein the dose is selected from the group consisting of from 60 mg to 500 mg; from 100 mg to 300 mg or from 125 mg to 150 mg.

58. A method according to any preceding embodiment wherein the dose is 62.5 mg, 125 mg, 150 mg, 250 mg or 500 mg.

59. A method according to any preceding embodiment wherein the dose is 125 mg or 150 mg.

60. A method according to any preceding embodiment wherein the dose is 125 mg.

61. A method according to any one of embodiments 1 to 59, wherein the dose is 150 mg.

62. A method according to any one of embodiments 1 to 58 wherein the dose is 62.5 mg.

63. A method according to any one of embodiments 1 to 58 wherein the dose is 250 mg.

64. A method according to any preceding embodiment wherein the dose is of up to 0.6 mg/kg, up to 0.7 mg/kg, up to 0.8 mg/kg, up to 0.9 mg/kg, up to 1 mg/kg, up to 1.1 mg/kg, up to 1.2 mg/kg, up to 1.3 mg/kg, up to 1.4 mg/kg, up to 1.5 mg/kg, up to 1.6 mg/kg, up to 1.7 mg/kg, up to 1.8 mg/kg, up to 1.9 mg/kg, up to 2 mg/kg, up to 2.1 mg/kg, up to 2.2 mg/kg, up to 2.3 mg/kg, up to 2.4 mg/kg, up to 2.5 mg/kg, up to 2.6 mg/kg, up to 2.7 mg/kg, up to 2.8 mg/kg, up to 2.9 mg/kg, up to 3 mg/kg, up to 4 mg/kg, up to 5 mg/kg, up to 6 mg/kg, up to 7 mg/kg, up to 8 mg/kg, up to 9 mg/kg, up to 10 mg/kg, up to 11 mg/kg or up to 12 mg/kg.

65. A method according to any preceding embodiment wherein the dose is of up to 6 mg/kg or up to 3 mg/kg.

66. A method according to any preceding embodiment wherein the dose is of at least 0.45 mg/kg, at least 0.5 mg/kg, at least 0.6 mg/kg, at least 0.7 mg/kg, at least 0.8 mg/kg, at least 0.9 mg/kg, at least 1 mg/kg, at least 1.1 mg/kg, at least 1.2 mg/kg, at least 1.3 mg/kg, at least 1.4 mg/kg, at least 1.5 mg/kg, at least 1.6 mg/kg, at least 1.7 mg/kg, at least 1.8 mg/kg, at least 1.9 mg/kg, at least 2 mg/kg, at least 2.1 mg/kg, at least 2.2 mg/kg, at least 2.3 mg/kg, at least 2.4 mg/kg, at least 2.5 mg/kg, at least 2.6 mg/kg, at least 2.7 mg/kg, at least 2.8 mg/kg, at least 2.9 mg/kg, at least 3 mg/kg, at least 4 mg/kg, at least 5 mg/kg, at least 6 mg/kg, at least 7 mg/kg, at least 8 mg/kg, at least 9 mg/kg, at least 10 mg/kg, at least 11 mg/kg, or at least 12 mg/kg.

67. A method according to any preceding embodiment wherein the dose is of at least 0.7 mg/kg or at least 1.4 mg/kg.

68. A method according to any preceding embodiment wherein the dose is selected from the group consisting of from 0.1 mg/kg to 12 mg/kg; from 0.4 mg/kg to 11 mg/kg; from 0.7 mg/kg to 10 mg/kg; from 1 mg/kg to 9 mg/kg; from 1.3 mg/kg to 8 mg/kg; from 1.6 mg/kg to 7 mg/kg; from 1.9 mg/kg to 6 mg/kg; from 2.2mg/kg to 5 mg/kg; from 2.5 mg/kg to 4 mg/kg; from 2.6 mg/kg to 3.8 mg/kg; from 2.7 mg/kg to 3.6 mg/kg; from 2.6 mg/kg to 3.4 mg/kg; from 2.7 mg/mg to 3.3 mg/kg; from 2.8 mg/kg to 3.2 mg/kg; and from 2.9 mg/kg to 3.1 mg/kg.

69. A method according to any preceding embodiment wherein the dose is selected from the group consisting of from 0.6 mg/kg to 11 mg/kg; from 0.7 mg/kg to 10 mg/kg; from 0.8 mg/kg to 9 mg/kg; from 0.9 mg/kg to 8 mg/kg; from 1 mg/kg to 7 mg/kg; from 1.1 mg/kg to 6 mg/kg; from 1.2 mg/kg to 5 mg/kg; from 1.3 mg/kg to 4 mg/kg; from 1.4 mg/kg to 3 mg/kg; from 1.5 mg/kg to 2.9 mg/kg; from 1.6 mg/kg to 2.8 mg/kg; from 1.7 mg/mg to 2.7 mg/kg; from 1.8 mg/kg to 2.6 mg/kg; from 1.9mg/kg to 2.5 mg/kg; from 2 mg/kg to 2.4 mg/kg; and from 2.1 mg/kg to 2.3 mg/kg.

70. A method according to any preceding embodiment wherein the dose is from 0.7 mg/kg to 6 mg/kg.

71. A method according to any preceding embodiment wherein the dose is from 1.4 mg/kg to 3 mg/kg.

72. A method according to any preceding embodiment comprising administering at least two injections of the antibody or fragment thereof.

73. The method of embodiment 72 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a second injection (C_{min}) is at least about 2.5 µg / ml.

74. A method according to any preceding embodiment comprising administering at least three injections of the antibody or fragment thereof.

75. The method of embodiment 74 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a second injection and prior to administration of a third injection (C_{min}) is at least about 0.5 µg/ml.

76. The method of any one of embodiments 74 to 75 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a third injection (C_{min}) is at least about 0.5 µg/ml.

77. A method according to any preceding embodiment comprising administering at least four injections of the antibody or fragment thereof.

78. The method of embodiment 77 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a third injection and prior to administration of a fourth injection (C_{min}) is at least about 0.5 µg/ml.

79. The method of any one of embodiments 77 to 78 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a first injection and prior to administration of a fourth injection (C_{min}) is at least about 0.5 µg/ml.

80. The method of any one of embodiments 77 to 79 wherein the minimum blood serum concentration reached by the antibody or fragment thereof after administration of a second injection and prior to administration of a fourth injection (C_{min}) is at least about 0.5 µg/ml.

81. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min}) is between 2.5 µg/ml and 600 µg/ml.

82. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min})is at least 2.5 µg/ml, 2.6 µg/ml, at least 2.7 µg/ml, at least 2.8 µg/ml, at least 2.9 µg/ml, at least 3 µg/ml, at least 3.1 µg/ml, at least 3.2 µg/ml, at least 3.3 µg/ml, at least 3.4 µg/ml, at least 3.5 µg/ml, at least 3.6 µg/ml, at least 3.7 µg/ml, at least 3.8 µg/ml, at least 3.9 µg/ml, at least 4 µg/ml, at least 4.1 µg/ml, at least 4.2 µg/ml, at least 4.3 µg/ml, at least 4.4 µg/ml, at least 4.5 µg/ml, at least 4.6 µg/ml, at least 4.7 µg/ml, at least 4.8 µg/ml, at least 4.9 µg/ml, at least 5 µg/ml, at least 5.1 µg/ml, at least 5.2 µg/ml, at least 5.3 µg/ml, at least 5.4 µg/ml, at least 5.5 µg/ml, at least 5.6 µg/ml, at least 5.7 µg/ml, at least 5.8 µg/ml, at least 5.9 µg/ml, at least 6 µg/ml, at least 6.5 µg/ml, at least 7 µg/ml, at least 7.5 µg/ml, at least 8 µg/ml, at least 8.5 µg/ml, at least 9 µg/ml, at least 9.5 µg/ml, at least 10 µg/ml, at least 11 µg/ml, at least 12 µg/ml, at least 13 µg/ml, at least 14 µg/ml, at least 15 µg/ml, at least 16 µg/ml, at least 17 µg/ml, at least 18 µg/ml, at least 19 µg/ml, at least 20 µg/ml, at least 25 µg/ml, at least 30 µg/ml, at least 35 µg/ml, at least 40 µg/ml, at least 50 µg/ml, at least 60 µg/ml, at least 70 µg/ml, at least 80 µg/ml, at least 90 µg/ml, or at least 100 µg/ml.

83. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min}) is at least about 4 µg/ml, at least about 5 µg/ml, or at least about 20 µg/ml.

84. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min})is up to 600 µg/ml, up to 500 µg/ml, up to 450 µg/ml, up to 400 µg/ml, up to 350 µg/ml, up to 300 µg/ml, up to 275 µg/ml, up to 250 µg/ml, up to 225 µg/ml, up to 200 µg/ml, up to 175 µg/ml, up to 150 µg/ml, up to 125 µg/ml, up to 100 µg/ml, up to 90 µg/ml, up to 80 µg/ml, up to 70 µg/ml, up to 60 µg/ml, up to 50 µg/ml, up to 45 µg/ml, up to 40 µg/ml, up to 35 µg/ml, up to 30 µg/ml, up to 25 µg/ml, up to 23 µg/ml, up to 20 µg/ml, up to 15 µg/ml, up to 10 µg/ml, up to 9 µg/ml, up to 8 µg/ml, up to 7 µg/ml, up to 6 µg/ml, up to 5 µg/ml, up to 4 µg/ml, up to 3 µg/ml, or up to 2.5 µg/ml..

85. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min})is up to about 50 µg/ml, up to about 25 µg/ml, up to about 15 µg/ml, or up to about 7 µg/ml.

86. The method of any preceding embodiment wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min})is selected from the group consisting of at least 3 µg/ml and up to 350 µg/ml; at least 10 µg/ml and up to 300 µg/ml; at least 12.5 µg/ml and up to 250 µg/ml; at least 15 µg/ml and up to 250 µg/ml; at least 18 µg/ml and up to 240 µg/ml; at least 20 µg/ml and up to 220 µg/ml; at least 25 µg/ml and up to 190 µg/ml; at least 30 µg/ml and up to 150 µg/ml; at least 35 µg/ml and up to 125 µg/ml; at least 40 µg/ml and up to 90 µg/ml; and at least 50 µg/ml and up to 65 µg/ml.

87. The method of any preceding embodiment wherein the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is at least about 1.5 µg / ml, at least about 2 µg / ml, at least about 5 µg / ml, at least about 10 µg / ml, at least about 20 µg / ml, at least about 30 µg / ml, at least about 40 µg / ml, at least about 50 µg / ml, at least about 60 µg / ml, at least about 70 µg / ml, at least about 80 µg / ml, at least about 90 µg / ml, at least about 100 µg / ml, at least about 150 µg / ml, at least about 200 µg / ml, at least about 300 µg / ml or at least about 550 µg / ml.

88. The method of any preceding embodiment wherein the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is up to about 550 µg / ml, up to about 400 µg / ml, up to about 300 µg / ml, up to about 200 µg / ml, up to about 150 µg / ml, up to about 100 µg / ml, up to about 90 µg / ml, up to about 80 µg / ml, up to about 70 µg / ml, up to about 60 µg / ml, up to about 50 µg / ml, up to about 45 µg / ml, up to about 40 µg / ml, up to about 35 µg / ml, up to about 30 µg / ml, up to about 25 µg / ml, up to about 23 µg / ml, up to about 20 µg / ml, up to about 15 µg / ml, or up to about 10 µg / ml.

89. The method of any preceding embodiment wherein the injection is subcutaneous and the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is 1.5 µg / ml to 275 µg / ml; 2 µg / ml to 200 µg / ml; 5 µg / ml to 150 µg / ml; 5 µg / ml to 100 µg / ml; 10 µg / ml to 80 µg / ml; 10 µg / ml to 25 µg / ml; 25 µg / ml to 50 µg / ml; or 35 µg / ml to 75 µg / ml.

90. The method of any preceding embodiment wherein the injection is intravenous and the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is 6 µg / ml to 550 µg / ml; 15 µg / ml to 400 µg / ml; 20 µg / ml to 300 µg / ml; 30 µg / ml to 200 µg / ml; 30 µg / ml to 90 µg / ml; 40 µg / ml to 105 µg / ml; 95 µg / ml to 150 µg / ml; or 95 µg / ml to 200 µg / ml.

91. The method of any preceding embodiment wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 4 µg/mL to about 15 µg/mL.

92. The method of any preceding embodiment wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 20 µg/mL to about 45 µg/mL.

93. The method of any preceding embodiment wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 5 µg/mL to about 23 µg/mL.

94. The method of any preceding embodiment wherein blood serum concentrations of the antibody or fragment thereof during treatment are around or below 10 µg/mL.

95. The method of any preceding embodiment wherein the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection may be at least around 100,000 ng/ml*day, 500,000 ng/ml*day, at least around 600,000 ng/ml*day, at least around 700,000 ng/ml*day, at least around 800,000 ng/ml*day, at least around 900,000 ng/ml*day, at least around 1,000,000 ng/ml*day, at least around 1,100,000 ng/ml*day, at least around 1,300,000 ng/ml*day, at least around 1,500,000 ng/ml*day, at least around 1,700,000 ng/ml*day, at least around 2,000,000 ng/ml*day, at least around 2,500,000 ng/ml*day, at least around 3,000,000 ng/ml*day, at least around 3,300,000 ng/ml*day or at least around 3,500,000 ng/ml*day, eg at least around 1,000,000 ng/ml*day or at least around 3,000,000 ng/ml*day.

96. The method of any preceding embodiment wherein the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection may be up to around 4,500,000 ng/ml*day, up to around 4,200,000 ng/ml*day, up to around 4,000,000 ng/ml*day, up to around 3,800,000 ng/ml*day, up to around 3,600,000 ng/ml*day, up to around 3,400,000 ng/ml*day, up to around 3,200,000 ng/ml*day, up to around 3,000,000 ng/ml*day, up to around 2,800,000 ng/ml*day, up to around 2,500,000 ng/ml*day, up to around 2,000,000

ng/ml*day, up to around 1,800,000 ng/ml*day, up to around 1,500,000 ng/ml*day, up to around 1,200,000 ng/ml*day or up to around 1,000,000 ng/ml*day, eg up to around 1,500,000 ng/ml*day or up to around 3,800,000 ng/ml*day.

97. The method of any preceding embodiment wherein the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be from around 100,000 ng/ml*day to around 4,500,000 ng/ml*day or around 1,000,000 ng/ml*day to around 3,800,000 ng/ml*day.

98. The method of any preceding embodiment wherein the antibody or fragment thereof is administered at most once every 12 weeks.

99. The method of any preceding embodiment wherein the antibody or fragment thereof is administered every 12 weeks or every 24 weeks.

100. The method of any preceding embodiment wherein the dose is 125 mg.

101. The method of any preceding embodiment wherein the dose is an initial dose of 250 mg followed by 125 mg.

102. The method of any preceding embodiment wherein the dose is 125 mg administered every 12 weeks.

103. The method of any preceding embodiment wherein the dose is an initial dose of 250 mg followed by 125 mg administered every 12 weeks.

104. The method of any preceding embodiment, comprising an induction phase and a maintenance phase.

105. The method of embodiment 104, wherein the induction phase comprises administering one or more induction phase injections of the antibody or fragment thereof, at an induction dose of between 20 and 500 mg; 20 mg and 300 mg; between 50 mg and 300 mg; between 100 mg and 300 mg; or between 150 mg and 300 mg.

106. The method of embodiment 104 wherein the induction dose is between 200 mg and 300 mg; or between 225 mg and 275 mg.

107. The method of embodiment 104 wherein the induction dose is about 500 mg, 250 mg, about 125 mg or about 62.5 mg.

108. The method of embodiment 104 wherein the induction dose is about 250 mg.

109. The method of any one of embodiments 104 to 108 wherein the induction phase is at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks or at least 24 weeks in duration.

110. The method of any one of embodiments 104 to 109 wherein the induction phase comprises administering two or more induction phase injections of the antibody or fragment thereof.

111. The method of embodiment 110 wherein each induction phase injection is administered at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks or at least 24 weeks apart.

112. The method of any one of embodiments 110 to 111 wherein each induction phase injection comprises the same mass of the antibody or fragment thereof as each other induction phase injection.

113. The method of any one of embodiments 110 to 111, wherein the first induction phase injection is at a loading dose and wherein the loading dose comprises up to three times the mass of the antibody or fragment thereof as each subsequent induction phase injection.

114. The method of any one of embodiments 110 to 111, wherein the first induction phase injection is at a loading dose and wherein the loading dose comprises up to twice the mass of the antibody or fragment thereof as each subsequent induction phase injection.

115. The method of any one of embodiments 110 to 111, wherein the first induction phase injection is at a loading dose and wherein the loading dose comprises up to 1.5 times the mass of the antibody or fragment thereof as each subsequent induction phase injection.

116. The method of embodiment any one of embodiments 113 to 115, wherein the loading dose is between 100 and 600 mg; between 150 and 550 mg; or between 200 and 500 mg.

117. The method of embodiment 116 wherein the loading dose is about 500 mg, about 250 mg or about 125mg.

118. The method of embodiment 117 wherein the loading dose is about 500 mg.

119. The method of any one of embodiments 110 to 118 wherein the second induction phase injection is administered 2 to 16 weeks after the first induction phase injection; administered 3 to 14 weeks after the first induction phase injection; or administered 4 to 12 weeks after the first induction phase injection.

120. The method of any one of embodiments 110 to 119 wherein the second induction phase injection is administered 2 to 14 weeks after the first induction phase injection; administered 2 to 12 weeks after the first induction phase injection; administered 2 to 10 weeks after the first induction phase injection; administered 2 to 8 weeks after the first induction phase injection; administered 2 to 7 weeks after the first induction phase injection; or administered 2 to 6 weeks after the first induction phase injection.

121. The method of any one of embodiments 110 to 120 wherein the second induction phase injection is administered 3 to 13 weeks after the first induction phase injection; administered 5 to 11 weeks after the first induction phase injection ; or administered 6 to 10 weeks after the first induction phase injection ; or administered 7 to 9 weeks after the first induction phase injection .

122. The method of any one of embodiments 110 to 121 wherein the second induction phase injection is administered 4 to 8 weeks after the first induction phase injection .

123. The method of any one of embodiments 110 to 122 wherein the second induction phase injection is administered about 4 weeks or about 8 weeks after the first induction phase injection.

124. The method of any one of embodiments 110 to 123 wherein the second induction phase injection is administered 4 weeks after the first induction phase injection.

125. The method of any one of embodiments 110 to 124 wherein the induction phase comprises administering three or more induction phase injections of the antibody or fragment thereof.

126. The method of embodiment 125 wherein the third induction phase injection is administered 2 to 16 weeks after the second induction phase injection; administered 3 to 14 weeks after the second induction phase injection; or administered 4 to 12 weeks after the second induction phase injection.

127. The method of any one of embodiments 125 to 126 wherein the third induction phase injection is administered 2 to 14 weeks after the second induction phase injection; administered 2 to 12 weeks after the second induction phase injection; administered 2 to 10 weeks after the second induction phase injection; administered 2 to 8 weeks after the second induction phase injection; administered 2 to 7 weeks after the second induction phase injection; or administered 2 to 6 weeks after the second induction phase injection.

128. The method of any one of embodiments 125 to 127 wherein the third induction phase injection is administered 3 to 13 weeks after the second induction phase injection; administered 5 to 11 weeks after the second induction phase injection; or administered 6 to 10 weeks after the second induction phase injection; or administered 7 to 9 weeks after the second induction phase injection.

129. The method of any one of embodiments 125 to 128 wherein the third induction phase injection is administered 4 to 8 weeks after the second induction phase injection.

130. The method of any one of embodiments 125 to 129 wherein the third induction phase injection is administered about 4 weeks or about 8 weeks after the second induction phase injection.

131. The method of any one of embodiments 125 to 130 wherein the third induction phase injection is administered 4 weeks after the second induction phase injection.

132. The method of any one of embodiments 125 to 131 wherein the interval between the first induction phase injection and the second induction phase injection has the same duration as the interval between the second induction phase injection and the third induction phase injection.

133. The method of any one of embodiments 125 to 132 wherein each induction phase injection comprises the same mass of the antibody or fragment thereof as each other induction phase

injection and/or wherein each interval between induction phase injections has the same duration as each other interval between induction phase injections.

134. The method of any one of embodiments 104 to 133, wherein the maintenance phase comprises administering one or more maintenance phase injections of the antibody or fragment thereof, at a maintenance dose between 20 mg and 300 mg; between 50 mg and 300 mg; between 100 mg and 300 mg; or between 150 mg and 300 mg.

135. The method of any one of embodiments 104 to 134 wherein the maintenance dose is between 200 mg and 300 mg; or between 225 mg and 275 mg.

136. The method of any one of embodiments 104 to 134 wherein the maintenance dose is about 500 mg, 250 mg, about 125 mg or about 62.5 mg.

137. The method of any one of embodiments 104 to 136 wherein the maintenance dose is about 250 mg.

138. The method of any one of embodiments 104 to 137 wherein the maintenance phase is at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks, at least 24 weeks, at least 32 weeks, at least 40 weeks, at least 52 weeks, or at least 100 weeks in duration.

139. The method of any one of embodiments 104 to 138 wherein the maintenance phase comprises administering two or more maintenance phase injections of the antibody or fragment thereof.

140. The method of embodiment 139 wherein each maintenance phase injection is administered at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 16 weeks, at least 24 weeks, at least 32 weeks, at least 40 weeks or at least 52 weeks apart.

141. The method of any one of embodiments 139 to 140 wherein each maintenance phase injection comprises the same mass of the antibody or fragment thereof as each other maintenance phase injection.

142. The method of any one of embodiments 139 to 141 wherein a second maintenance phase injection is administered 2 to 16 weeks after a first maintenance phase injection; administered

3 to 14 weeks after a first maintenance phase injection; or administered 4 to 12 weeks after a first maintenance phase injection.

143. The method of any one of embodiments 139 to 142 wherein a second maintenance phase injection is administered 2 to 14 weeks after a first maintenance phase injection; administered 2 to 12 weeks after a first maintenance phase injection; administered 2 to 10 weeks after a first maintenance phase injection; administered 2 to 8 weeks after a first maintenance phase injection; administered 2 to 7 weeks after a first maintenance phase injection; or administered 2 to 6 weeks after a first maintenance phase injection.

144. The method of any one of embodiments 139 to 143 wherein a second maintenance phase injection is administered 3 to 13 weeks after a first maintenance phase injection; administered 5 to 11 weeks after a first maintenance phase injection; or administered 6 to 10 weeks after a first maintenance phase injection; or administered 7 to 9 weeks after a first maintenance phase injection.

145. The method of any one of embodiments 139 to 144 wherein a second maintenance phase injection is administered 4 to 8 weeks after a first maintenance phase injection.

146. The method of any one of embodiments 139 to 145 wherein a second maintenance phase injection is administered about 4 weeks or about 8 weeks after a first maintenance phase injection.

147. The method of any one of embodiments 139 to 146 wherein a second maintenance phase injection is administered about 4 weeks after a first maintenance phase injection.

148. The method of embodiment any one of embodiments 139 to 147 wherein the maintenance phase comprises administering three or more maintenance phase injections of the antibody or fragment thereof.

149. The method of embodiment 148 wherein the third maintenance phase injection is administered 2 to 16 weeks after the second maintenance phase injection; administered 3 to 14 weeks after the second maintenance phase injection; or administered 4 to 12 weeks after the second maintenance phase injection.

150. The method of any one of embodiments 148 to 149 wherein the third maintenance phase injection is administered 2 to 14 weeks after the second maintenance phase injection;

administered 2 to 12 weeks after the second maintenance phase injection; administered 2 to 10 weeks after the second maintenance phase injection; administered 2 to 8 weeks after the second maintenance phase injection; administered 2 to 7 weeks after the second maintenance phase injection; or administered 2 to 6 weeks after the second maintenance phase injection.

151. The method of any one of embodiments 148 to 150 wherein the third maintenance phase injection is administered 3 to 13 weeks after the second maintenance phase injection; administered 5 to 11 weeks after the second maintenance phase injection; or administered 6 to 10 weeks after the second maintenance phase injection; or administered 7 to 9 weeks after the second maintenance phase injection.

152. The method of any one of embodiments 148 to 151 wherein the third maintenance phase injection is administered 4 to 8 weeks after the second maintenance phase injection.

153. The method of any one of embodiments 148 to 152 wherein the third maintenance phase injection is administered about 4 weeks or about 8 weeks after the second maintenance phase injection.

154. The method of any one of embodiments 148 to 153 wherein the interval between the first maintenance phase injection and the second maintenance phase injection has the same duration as the interval between the second maintenance phase injection and the third maintenance phase injection.

155. The method of any one of embodiments 148 to 154 wherein each maintenance phase injection comprises the same mass of the antibody or fragment thereof as each other maintenance phase injection and/or wherein each interval between maintenance phase injections has the same duration as each other interval between maintenance phase injections.

156. The method of any one of embodiments 104 to 155, wherein the interval between two or more maintenance phase injections has an equal duration than or a longer duration than the interval between two or more induction phase injections.

157. The method of any one of embodiments 104 to 156, wherein the interval between the first maintenance phase injection and the second maintenance phase injection has an equal duration than or a longer duration than the interval between two or more induction phase injections.

158. The method of any one of embodiments 104 to 157, wherein the interval between two or more induction phase injections is about 2 weeks, about 4 weeks or about 8 weeks and the interval between two or more maintenance phase injections is about 12 weeks or about 16 weeks.

159. The method of any one of embodiments 104 to 158, wherein the interval between two or more induction phase injections is about 4 weeks or about 8 weeks and the interval between two or more maintenance phase injections is about 12 weeks.

160. The method of any one of embodiments 104 to 158, wherein the interval between two or more induction phase injections is about 4 weeks and the interval between two or more maintenance phase injections is about 16 weeks.

161. The method of any one of embodiments 104 to 159, wherein the interval between two or more induction phase injections is about 4 weeks and the interval between two or more maintenance phase injections is about 12 weeks.

162. The method of any one of embodiments 104 to 157, wherein the interval between two or more induction phase injections is about 4 weeks and the interval between two or more maintenance phase injections is about 4 weeks.

163. The method of any one of embodiments 104 to 157, wherein the interval between two or more induction phase injections is about 8 weeks and the interval between two or more maintenance phase injections is about 8 weeks.

164. The method of any one of embodiments 104 to 157, wherein the interval between two or more induction phase injections is about 2 weeks and the interval between two or more maintenance phase injections is about 8 weeks.

165. The method of any one of embodiments 104 to 164, wherein the interval between three or more induction phase injections is constant.

166. The method of any one of embodiments 104 to 165, wherein the interval between three or more maintenance phase injections varies.

167. The method of any one of embodiments 104 to 166, wherein the combined duration of the induction phase and the mantenance phase is at least 52 weeks.

168. The method of any one of embodiments 104 to 167, wherein the subject is transitioned from the induction phase to the maintenance phase based on:

(a) clinical response; and/or

(b) the time since the administration of the first induction phase injection.

169. The method of embodiment 168, wherein the clinical response is assessed at 16 weeks after the administration of the first induction phase injection.

170. The method of any one of embodiments 168 to 169, wherein the clinical response is achieving EASI50, EASI75, EASI90 or EASI100.

171. The method of any one of embodiments 168 to 170, wherein the clinical response is achieving IGA-AD0/1 and/or a reduction of at least 2 IGA-AD points.

172. The method of any one of embodiments 168 to 171, wherein the clinical response is achieving a reduction of at least 3 NRS points or at least 4 NRS points.

173. The method of any one of embodiments 168 to 172, wherein the transition from the induction phase to the maintenance phase takes place 16 or more weeks after the administration of the first induction phase injection.

174. The method of any one of embodiments 168 to 173, wherein the transition from the induction phase to the maintenance phase takes place 24 or more weeks after the administration of the first induction phase injection.

175. The method of any one of embodiments 168 to 174, wherein the transition from the induction phase to the maintenance phase takes place up to one year after the administration of the first induction phase injection.

176. The method of any one of embodiments 168 to 174, wherein the transition from the induction phase to the maintenance phase takes place 16 to 24 weeks after the administration of the first induction phase injection.

177. The method of any one of embodiments 168 to 176, wherein the transition from the induction phase to the maintenance phase takes place 24 weeks after the administration of the first induction phase injection, if the subject has achieved a clinical response of at least EASI75 at 16 weeks.

178. The method of any preceding embodiment wherein the administration is subcutaneous.

179. The method of embodiment 178 wherein the induction phase comprises administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

180. The method of any one of embodiments 178 or 179 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

181. The method of embodiment 178 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

182. The method of any one of embodiments 178 or 181 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

183. The method of embodiment 178 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

184. The method of any one of embodiments 178 or 183 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 125 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

185. The method of embodiment 178 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

186. The method of any one of embodiments 178 or185 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 62.5 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

187. The method of any one of embodiments 179 to 186 comprising administering at least six induction phase injections or at least seven induction phase injections.

188. The method of any one of embodiments 179 to 187 wherein the first maintenance phase injection is administered from 4 weeks to 24 weeks or 4 weeks to 16 weeks after the final induction phase injection.

189. The method of any one of embodiments 179 to 188 wherein the first maintenance phase injection is administered 12 weeks after the final induction phase injection.

190. The method of any one of embodiments 179 to 189 wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered from 4 weeks to 24 weeks or 4 weeks to 16 weeks after the preceding maintenance phase injection.

191. The method of any one of embodiments 179 to 190 wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 12 weeks after the preceding maintenance phase injection.

192. The method of any one of embodiments 179 to 191

(a) comprising administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered at least 4 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

193. The method of any one of embodiments 179 to 191

(a) comprising administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 12 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 12 weeks after the preceding maintenance phase injection.

194. The method of any one of embodiments 179 to 191

(a) comprising administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 16 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 16 weeks after the preceding maintenance phase injection.

195. The method of any one of embodiments 179 to 191

(a) comprising administering at least seven induction phase injections;

(b) wherein the first maintenance phase injection is administered 24 weeks after the final induction phase injection; and

(c) wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 24 weeks after the preceding maintenance phase injection.

196. The method of any preceding embodiment wherein the antibody or fragment thereof is capable of exhibiting one or more pharmacokinetic properties selected from the group consisting of:

(a) a rate of clearance (CL) of about 0.05 to about 0.18 L/day;

(b) an absorption constant (ka) of about 0.11 to about 0.33 L/day;

(c) a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L;

(d) a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L;

(e) a rate of clearance from the central compartment to the second compartment (Q) of about 0.31 to about 0.93 L/day; and

(f) a bioavailability (Fabs1) of about 0.6 to about 1.0.

197. The method of embodiment 196, wherein the antibody or fragment thereof has 1, 2, 3, 4, 5, or 6 of the pharmacokinetic properties listed in (a) to (f).

198. The method of any one of embodiments 196 to 197, wherein the antibody or fragment thereof exhibits a rate of clearance (CL) of about 0.05 to about 0.18 L/day; about 0.06 to about 0.17 L/day; about 0.07 to about 0.16 L/day; about 0.08 to about 0.15 L/day; about 0.09 to about 0.14 L/day; or about 0.10 to about 0.13 L/day.

199. The method of any one of embodiments 196 to 198, wherein the antibody or fragment thereof exhibits a rate of clearance (CL) of about 0.115 L/day.

200. The method of any one of embodiments 196 to 199, wherein the antibody or fragment thereof exhibits an absorption constant (ka) of about 0.11 to about 0.33 L/day; about 0.12 to about 0.32 L/day; about 0.13 to about 0.31 L/day; about 0.14 to about 0.30 L/day; about 0.15 to about 0.29 L/day; about 0.16 to about 0.28 L/day; about 0.17 to about 0.27 L/day; about 0.18 to about 0.26 L/day; about 0.19 to about 0.25 L/day; about 0.20 to about 0.24 L/day; or about 0.21 to about 0.23 L/day.

201. The method of any one of embodiments 196 to 200, wherein the antibody or fragment thereof exhibits an absorption constant (ka) of about 0.22 L/day.

202. The method of any one of embodiments 196 to 201, wherein the antibody or fragment thereof exhibits a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L; about 1.8

to about 4.8 L; about 2.0 to about 4.6 L; about 2.2 to about 4.4 L; about 2.4 to about 4.2 L; about 2.6 to about 4.0 L; about 2.8 to about 3.8 L; about 3.0 to about 3.6 L; or about 3.2 to about 3.4 L.

203. The method of any one of embodiments 196 to 202, wherein the antibody or fragment thereof exhibits a volume of central compartment volume (Vc) of about 3.3 L.

204. The method of any one of embodiments 196 to 203, wherein the antibody or fragment thereof exhibits a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L; about 1.4 to about 3.4 L; about 1.6 to about 3.2 L; about 1.8 to about 3.0 L; about 2.0 to about 2.8 L; about 2.2 to about 2.6 L; or about 2.3 to about 2.5 L.

205. The method of any one of embodiments 196 to 204, wherein the antibody or fragment thereof exhibits a second (peripheral compartment) volume (Vp1) of about 2.4 L.

206. The method of any one of embodiments 196 to 205, wherein the antibody or fragment thereof exhibits a rate of clearance from the central compartment to the second compartment (Q1) of about 0.31 to about 0.93 L/day; about 0.36 to about 0.88 L/day; about 0.41 to about 0.83 L/day; about 0.46 to about 0.78 L/day; about 0.51 to about 0.73 L/day; about 0.56 to about 0.68 L/day; about 0.60 to about 0.64 L/day; or about 0.61 to about 0.63 L/day.

207. The method of any one of embodiments 196 to 206, wherein the antibody or fragment thereof exhibits a rate of clearance from the central compartment to the second compartment (Q1) of about 0.62 L/day.

208. The method of any one of embodiments 196 to 207, wherein the antibody or fragment thereof exhibits a bioavailability (Fabs1) of about 0.6 to about 1.0; about 0.65 to about 0.95; about 0.70 to about 0.90; or about 0.75 to about 0.85.

209. The method of any one of embodiments 196 to 208, wherein the antibody or fragment thereof exhibits a bioavailability (Fabs1) of about 0.8.

210. The method of any one of embodiments 196 to 209, wherein said pharmacokinetic properties are determined using a two-compartment model.

211. The method of embodiment 210 wherein the two-compartment model is a linear two-compartment model.

212. The method of any preceding embodiment further comprising obtaining one or more blood samples from the subject and optionally measuring the blood serum concentration reached by the antibody or fragment thereof.

213. The method of any preceding embodiment, wherein the subject has an age selected from the group consisting of up to 6 years of age; from 6 years of age to 12 years of age; from 12 years of age to 18 years of age; at least 18 years of age; and less than 75 years of age.

214. The method of any preceding embodiment, wherein the subject is at least 18 years of age and/or less than 75 years of age.

215. The method of any preceding embodiment, wherein the Atopic Dermatitis is moderate-to-severe Atopic Dermatitis.

216. The method of any preceding embodiment, wherein the subject was diagnosed with Atopic Dermatitis at least one year before administration of the antibody or fragment thereof.

217. The method of any preceding embodiment, wherein the subject is a chronic Atopic Dermatitis patient.

218. The method of any preceding embodiment, wherein the antibody or fragment thereof is a second line treatment.

219. The method of any preceding embodiment, wherein the Atopic Dermatitis is not adequately controlled with topical prescription and/or systemic therapies or when those therapies are not advisable.

220. The method of any preceding embodiment, wherein the Atopic Dermatitis is resistant, non responsive or inadequately responsive to treatment by either topical corticosteroids and/or systemic therapies or when those therapies are not advisable or wherein the subject has had an inadequate response to, was intolerant to, or is refractory to one or more topical corticosteroids.

221. The method of any preceding embodiment, wherein the Atopic Dermatitis is not adequately controlled or inadequately responsive to treatment by topical corticosteroids.

222. The method of any preceding embodiment, wherein the subject is also being treated with one or more topical corticosteroids and/or wherein the antibody or fragment thereof is used with topical corticosteroids.

223. The method of any preceding embodiment, wherein the subject was previously treated with one or more topical corticosteroid.

224. A method according to any preceding embodiment further comprising administering a therapeutically effective amount of one or more topical corticosteroid.

225. A method according to embodiment 224 wherein the one or more topical corticosteroid is administered prior to the anti-OX40L antibody, or antigen-binding fragment thereof.

226. A method according to embodiment 225 wherein a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof is administered on the day that the subject discontinues treatment with the one or more topical corticosteroid.

227. A method according to embodiment 226 wherein the subject discontinues treatment with the one or more topical corticosteroid at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first administration of the one or more topical corticosteroid.

228. A method according to embodiment 224 wherein the one or more topical corticosteroid is administered after the anti-OX40L antibody, or antigen-binding fragment thereof.

229. A method according to embodiment 228 wherein a first administration of the one or more topical corticosteroid is administered on the day that the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

230. A method according to embodiment 229 wherein the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof, at least 2 months, at least 3

months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof.

231. A method according to any one of embodiments 226 and 229 wherein the one or more topical corticosteroid and the anti-OX40L antibody, or antigen-binding fragment thereof are administered sequentially and a period between administering an administration of the one or more topical corticosteroid and an injection of the anti-OX40L antibody, or antigen-binding fragment thereof is at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks, at least 40 weeks, at least 44 weeks, at least 48 weeks or at least 52 weeks.

232. A method according to embodiment 224 wherein the one or more topical corticosteroid is administered concurrently with the anti-OX40L antibody, or antigen-binding fragment thereof.

233. The method of any one of embodiments 220 to 232 wherein the topical corticosteroid is selected from the group consisting of betamethasone dipropionate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, diflorasone diacetate, halobetasol propionate, amcinonide, augmented betamethasone dipropionate, fluocinonide, halcinonide, triamcinolone acetonide, betamethasone valerate, clocortolone pivalate, desoximetasone, fluocinolone acetonide, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone valerate, prednicarbate, alclometasone dipropionate, desonide, hydrocortisone and hydrocortisone acetate.

234. The method of any one of embodiments 220 to 233 wherein the topical corticosteroid is selected from the group consisting of betamethasone dipropionate, betamethasone dipropionate;gentamicin sulphate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate and mometasone furoate.

235. The method of any one of embodiments 220 to 234 wherein the topical corticosteroid is betamethasone dipropionate, optionally wherein the betamethasone dipropionate is combined with gentamicin sulphate.

236. The method of any one of embodiments 220 to 235 wherein the topical corticosteroid is formulated as a cream, ointment, gel, foam, solution, lotion or gel.

237. The method of any one of embodiments 220 to 236 wherein the topical corticosteroid is applied twice daily or once daily.

238. The method of any one of embodiments 220 to 236 wherein the topical corticosteroid is applied once weekly or twice weekly.

239. The method of any preceding embodiment, wherein the Atopic Dermatitis is resistant, non responsive or inadequately responsive to treatment by either topical calcineurin inhibitors and/or systemic therapies or when those therapies are not advisable or wherein the subject has had an inadequate response to, was intolerant to, or is refractory to one or more topical calcineurin inhibitors .

240. The method of any preceding embodiment, wherein the Atopic Dermatitis is not adequately controlled or inadequately responsive to treatment by topical calcineurin inhibitors.

241. The method of any preceding embodiment, wherein the subject is also being treated with one or more topical calcineurin inhibitor and/or wherein the antibody or fragment thereof is used with one or more topical calcineurin inhibitor.

242. The method of any preceding embodiment, wherein the subject was previously treated with one or more topical calcineurin inhibitor.

243. A method according to any preceding embodiment further comprising administering a therapeutically effective amount of one or more topical calcineurin inhibitor.

244. A method according to embodiment 243 wherein the one or more topical calcineurin inhibitor is administered prior to the anti-OX40L antibody, or antigen-binding fragment thereof.

245. A method according to embodiment 244 wherein a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof is administered on the day that the subject discontinues treatment with the one or more topical calcineurin inhibitor.

246. A method according to embodiment 245 wherein the subject discontinues treatment with the one or more topical calcineurin inhibitor at least 2 months, at least 3 months, at least four

months, at least 5 months, at least 6 months or 4 to 6 months after administering a first administration of the one or more topical calcineurin inhibitor.

247. A method according to embodiment 243 wherein the one or more topical calcineurin inhibitor is administered after the anti-OX40L antibody, or antigen-binding fragment thereof.

248. A method according to embodiment 247 wherein a first administration of the one or more topical calcineurin inhibitor is administered on the day that the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof.

249. A method according to embodiment 248 wherein the subject discontinues treatment with the anti-OX40L antibody, or antigen-binding fragment thereof, at least 2 months, at least 3 months, at least four months, at least 5 months, at least 6 months or 4 to 6 months after administering a first injection of the anti-OX40L antibody, or antigen-binding fragment thereof.

250. A method according to any one of embodiments 244 and 247 wherein the one or more topical calcineurin inhibitor and the anti-OX40L antibody, or antigen-binding fragment thereof are administered sequentially and a period between administering an administration of the one or more topical calcineurin inhibitor and an injection of the anti-OX40L antibody, or antigen-binding fragment thereof is at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks, at least 40 weeks, at least 44 weeks, at least 48 weeks or at least 52 weeks.

251. A method according to embodiment 243 wherein the one or more topical calcineurin inhibitor is administered concurrently with the anti-OX40L antibody, or antigen-binding fragment thereof.

252. The method of any one of embodiments 239 to 251 wherein the topical calcineurin inhibitor is tacrolimus ointment or pimecrolimus cream, e.g., tacrolimus ointment.

253. The method of any one of embodiments 239 to 252 wherein the topical calcineurin inhibitor is applied twice daily or once daily.

254. The method of any one of embodiments 239 to 253 wherein the topical calcineurin inhibitor is applied two to three times weekly.

255. The method of any preceding embodiment, wherein the subject is also being treated with one or more topical antihistamine and/or wherein the antibody or fragment thereof is used with one or more topical antihistamine.

256. The method of any preceding embodiment, wherein the subject is also being treated with one or more oral steroid and/or wherein the antibody or fragment thereof is used with one or more oral steroid.

257. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline EASI score.

258. The method of embodiment 257 wherein the determining a baseline EASI score comprises:

(a) Selecting a body region from the group consisting of head and neck; trunk including the genital area; upper extremities; and lower extremities including the buttocks;

(b) Assessing the extent of atopic dermatitis in the selected body region and assigning a region score based on the extent of atopic dermatitis in the selected body region;

(c) Assessing the severity of each of the following signs in the selected body region:

1. Erythema,
2. Edema and/or papulation,
3. Excoriation, and
4. Licenification,

and assigning a severity score to each sign in the selected body region;

(d) Determining a total score for the selected body region based on the region score and the severity score for each sign in the selected body region;

(e) Repeating steps (b) to (d) for each of the remaining body regions; and

(f) Determining a baseline EASI score based on the total score for each body region.

259. The method of any one of embodiments 257 to 258, wherein the baseline EASI score is at least 12.1, at least 16.1, or at least 21.1.

260. The method of any one of embodiments 257 to 259, wherein the baseline EASI score is at least 16.1.

261. The method of any one of embodiments 257 to 260, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline EASI score is determined.

262. The method of any one of embodiments 257 to 261, further comprising determining the baseline EASI score.

263. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration EASI score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

264. The method of any preceding embodiment wherein the post-administration EASI score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

265. The method of any preceding embodiment wherein the post-administration EASI score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

266. The method of any preceding embodiment wherein the post-administration EASI score is determined at the end of the induction phase.

267. The method of any preceding embodiment wherein the post-administration EASI score is less than or equal to 21.0.

268. The method of any preceding embodiment wherein the post-administration EASI score is less than or equal to 16.0.

269. The method of any preceding embodiment wherein the post-administration EASI score is less than or equal to 16.0, less than or equal to 15.0, less than or equal to 14.0, less than or equal to 13.0, less than or equal to 12.0, less than or equal to 11.0, less than or equal to 10.0, less than or equal to 9.0, less than or equal to 8.0, less than or equal to 7.0, less than or equal to 6.0, less than or equal to 5.0, less than or equal to 4.0, less than or equal to 3.0, less than or equal to 2.0, less than or equal to 1.0 or around 0.

270. The method of any preceding embodiment wherein the post-administration EASI score is less than or equal to 7.0 or less than or equal to 1.0.

271. The method of any preceding embodiment wherein the post-administration EASI score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline EASI score.

272. The method of any preceding embodiment wherein the post-administration EASI score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

273. The method of any preceding embodiment wherein the post-administration EASI score is reduced at least 6 points, at least 6.6 points, at least 7 points, at least 8 points, at least 9 points or at least 10 points relative to the baseline EASI score.

274. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration EASI score.

275. The method of any preceding embodiment wherein the one or more further post-administration EASI score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

276. The method of any preceding embodiment wherein the one or more further post-administration EASI score is determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

277. The method of any preceding embodiment wherein the one or more further post-administration EASI score is determined at the end of the induction phase.

278. The method of any preceding embodiment wherein the one or more further post-administration EASI score is less than or equal to 21.0.

279. The method of any preceding embodiment wherein the one or more further post-administration EASI score is less than or equal to 16.0, less than or equal to 15.0, less than or equal to 14.0, less than or equal to 13.0, less than or equal to 12.0, less than or equal to 11.0, less than or equal to 10.0, less than or equal to 9.0, less than or equal to 8.0, less than or equal to 7.0, less than or equal to 6.0, less than or equal to 5.0, less than or equal to 4.0, less than or equal to 3.0, less than or equal to 2.0, less than or equal to 1.0 or around 0.

280. The method of any preceding embodiment wherein the one or more further post-administration EASI score is less than or equal to 7.0 or less than or equal to 1.0.

281. The method of any preceding embodiment wherein the one or more further post-administration EASI score is reduced at least 10 percent, at least 25 percent or at least 50 percent relative to the baseline EASI score.

282. The method of any preceding embodiment wherein the one or more further post-administration EASI score is reduced at least 6 points, at least 6.6 points, at least 7 points, at least 8 points, at least 9 points or at least 10 points relative to the baseline EASI score.

283. The method of an any preceding embodiment wherein determining the post-administration EASI score and/or the one or more further post-administration EASI score comprises:

(a) Selecting a body region from the group consisting of head and neck; trunk including the genital area; upper extremities; and lower extremities including the buttocks;

(b) Assessing the extent of atopic dermatitis in the selected body region and assigning a region score based on the extent of atopic dermatitis in the selected body region;

(c) Assessing the severity of each of the following signs in the selected body region:

1. Erythema,
2. Edema and/or papulation,
3. Excoriation, and
4. Licenification,

and assigning a severity score to each sign in the selected body region;

(d) Determining a total score for the selected body region based on the region score and the severity score for each sign in the selected body region;

(e) Repeating steps (b) to (d) for each of the remaining body regions; and

(f) Determining a baseline EASI score based on the total score for each body region.

284. The method of any preceding embodiment wherein the post-administration EASI and/or further post-administration EASI is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

285. The method of any preceding embodiment wherein the post-administration EASI and/or further post-administration EASI is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

286. The method of any preceding embodiment wherein the post-administration EASI and/or further post-administration EASI is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

287. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the EASI score by at least 40% after the third injection as a treatment dose and wherein the reduction in EASI score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

288. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline IGA-AD score.

289. The method of embodiment 288 wherein the determining a baseline IGA-AD score comprises describing the overall appearance of AD lesions at a given time point by:

(f) Assigning a score of 0 – clear – when the most applicable morphological description is:
- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(g) Assigning a score of 1 – almost clear – when the most applicable morphological description is:
- Barely perceptible erythema, and/or barely perceptible induration/papulation, no oozing or crusting;

(h) Assigning a score of 2 – mild – when the most applicable morphological description is:
- Slight but definite erythema (pink), and/or slight but definite induration/papulation; no oozing or crusting;

(i) Assigning a score of 3 – moderate – when the most applicable morphological description is:
- Clearly perceptible erythema (dull red), and/or clearly perceptible induration/papulation; oozing and crusting may be present;

(j) Assigning a score of 4 – severe – when the most applicable morphological description is:
- Marked erythema (deep or bright red), and/or marked induration/papulation; disease is widespread in extent; oozing or crusting may be present.

290. The method of any one of embodiments 288 to 289, wherein the baseline IGA-AD score is 3 or 4.

291. The method of any one of embodiments 288 to 290, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline IGA-AD score is determined.

292. The method of any one of embodiments 288 to 291, further comprising determining the baseline IGA-AD score.

293. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration IGA-AD score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

294. The method of any preceding embodiment wherein the post-administration IGA-AD score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

295. The method of any preceding embodiment wherein the post-administration IGA-AD score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

296. The method of any preceding embodiment wherein the post-administration IGA-AD score is determined at the end of the induction phase.

297. The method of any preceding embodiment wherein the post-administration IGA-AD score is 0 or 1.

298. The method of any preceding embodiment wherein the post-administration IGA-AD score is reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline IGA-AD score.

299. The method of any preceding embodiment wherein the post-administration IGA-AD score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline IGA-AD score.

300. The method of any preceding embodiment wherein the post-administration IGA-AD score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

301. The method any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration IGA-AD score.

302. The method of any preceding embodiment wherein the one or more further post-administration IGA-AD score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

303. The method of any preceding embodiment wherein the one or more further post-administration IGA-AD score is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

304. The method of any preceding embodiment wherein the one or more further post-administration IGA-AD score is determined at the end of the induction phase.

305. The method of any preceding embodiment wherein the one or more further post-administration IGA-AD score is 0 or 1.

306. The method of any preceding embodiment wherein the one or more further post-administration IGA-AD score is reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline IGA-AD score.

307. The method of any preceding embodiment wherein determining the post-administration IGA-AD score and/or the one or more further post-administration IGA-AD score comprises describing the overall appearance of AD lesions at a given time point by:

(f) Assigning a score of 0 – clear – when the most applicable morphological description is:

- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(g) Assigning a score of 1 – almost clear – when the most applicable morphological description is:

- Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification; no oozing or crusting;

(h) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification; no oozing or crusting;

(i) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification; oozing and crusting may be present;

(j) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification; disease is widespread in extent; oozing or crusting may be present.

308. The method of any preceding embodiment wherein the post-administration IGA-AD and/or further post-administration IGA-AD is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration IGA-AD and/or further post-administration IGA-AD is:

(c) A IGA-AD score of 0 or 1, and/or

(d) reduced at least 2 points relative to the baseline IGA-AD score.

309. The method of any preceding embodiment wherein the post-administration IGA-AD and/or further post-administration IGA-AD is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration IGA-AD and/or further post-administration IGA-AD is:

(c) A IGA-AD score of 0 or 1, and/or

(d) reduced at least 2 points relative to the baseline IGA-AD score.

310. The method of any preceding embodiment wherein the post-administration IGA-AD and/or further post-administration IGA-AD is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration IGA-AD and/or further post-administration IGA-AD is:

(c) A IGA-AD score of 0 or 1, and/or

(d) reduced at least 2 points relative to the baseline IGA-AD score.

311. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the IGA-AD score by at least 2 points after the third injection as a treatment dose and wherein the reduction in IGA-AD score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

312. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline vIGA-AD score.

313. The method of embodiment 312 wherein the determining a baseline vIGA-AD score comprises describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:
- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:
- Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:
- Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:
- Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:
- Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification; disease is widespread in extent; oozing or crusting may be present.

314. The method of any one of embodiments 312 to 313, wherein the baseline vIGA-AD score is 3 or 4.

315. The method of any one of embodiments 312 to 314, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline vIGA-AD score is determined.

316. The method of any one of embodiments 312 to 315, further comprising determining the baseline vIGA-AD score.

317. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration vIGA-AD score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

318. The method of any preceding embodiment wherein the post-administration vIGA-AD score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

319. The method of any preceding embodiment wherein the post-administration vIGA-AD score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

320. The method of any preceding embodiment wherein the post-administration vIGA-AD score is determined at the end of the induction phase.

321. The method of any preceding embodiment wherein the post-administration vIGA-AD score is 0 or 1.

322. The method of any preceding embodiment wherein the post-administration vIGA-AD score is reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline vIGA-AD score.

323. The method of any preceding embodiment wherein the post-administration vIGA-AD score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline vIGA-AD score.

324. The method of any preceding embodiment wherein the post-administration vIGA-AD score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

325. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration vIGA-AD score.

326. The method of any preceding embodiment wherein the one or more further post-administration vIGA-AD score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

327. The method of any preceding embodiment wherein the one or more further post-administration vIGA-AD score is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

328. The method of any preceding embodiment wherein the one or more further post-administration vIGA-AD score is determined at the end of the induction phase.

329. The method of any preceding embodiment wherein the one or more further post-administration vIGA-AD score is 0 or 1.

330. The method of any preceding embodiment wherein the one or more further post-administration vIGA-AD score is reduced at least 1 point, at least 2 points, at least 3 points or up to 4 points relative to the baseline vIGA-AD score.

331. The method of any preceding embodiment wherein determining the post-administration vIGA-AD score and/or the one or more further post-administration vIGA-AD score comprises describing the overall appearance of AD lesions at a given time point by:

(a) Assigning a score of 0 – clear – when the most applicable morphological description is:
- No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting); post-inflammatory hyperpigmentation and/or hypopigmentation may be present;

(b) Assigning a score of 1 – almost clear – when the most applicable morphological description is:
- Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification; no oozing or crusting;

(c) Assigning a score of 2 – mild – when the most applicable morphological description is:

- Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification; no oozing or crusting;

(d) Assigning a score of 3 – moderate – when the most applicable morphological description is:

- Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification; oozing and crusting may be present;

(e) Assigning a score of 4 – severe – when the most applicable morphological description is:

- Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification; disease is widespread in extent; oozing or crusting may be present.

332. The method of any preceding embodiment wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

333. The method of any preceding embodiment wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

334. The method of any preceding embodiment wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

335. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the vIGA-AD score by at least 2 points after the third injection as a treatment dose and wherein the reduction in vIGA-AD score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

336. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline NRS score.

337. The method of embodiment 336 wherein the determining a baseline NRS score comprises the subject providing a numerical rating of their worst itch in the past 24 hours on a scale of 0 to 10, wherein "0" is no itch and "10" is the worst imaginable itch.

338. The method of embodiment 337 wherein the determining a baseline NRS score comprises the patient providing a numerical rating of their worst itch in the past 24 hours according to embodiment 337 once per day for 7 days and taking the average numerical rating as the baseline NRS score.

339. The method of any one of embodiments 336 to 338, wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

340. The method of any one of embodiments 336 to 339, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline NRS score is determined.

341. The method of any one of embodiments 336 to 340, further comprising determining the baseline NRS score.

342. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration NRS (numerical rating scale) score after administering a first injection of the antibody or fragment thereof.

343. The method of any preceding embodiment wherein the post-administration NRS score is determined within 2 hours, within 6 hours, within 12 hours, within 24 hours, within 24 hours, or within 7 days of administering a first injection of the antibody or fragment thereof.

344. The method of any preceding embodiment wherein the post-administration NRS score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

345. The method of any preceding embodiment wherein the post-administration NRS score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

346. The method of any preceding embodiment wherein the post-administration NRS score is determined at the end of the induction phase.

347. The method of any preceding embodiment wherein the post-administration NRS score is 0 to 7.

348. The method of any preceding embodiment wherein the post-administration NRS score is reduced at least 1 point, at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline NRS score.

349. The method of any preceding embodiment wherein the post-administration NRS score is reduced at least 2 points, at least 3 points or at least 4 points relative to the baseline NRS score.

350. The method of any preceding embodiment wherein the post-administration NRS score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline NRS score.

351. The method of any preceding embodiment wherein the post-administration NRS score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

352. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration NRS score.

353. The method of any preceding embodiment wherein the one or more further post-administration NRS score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

354. The method of any preceding embodiment wherein the one or more further post-administration NRS score is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

355. The method of any preceding embodiment wherein the one or more further post-administration NRS score is determined at the end of the induction phase.

356. The method of any preceding embodiment wherein the one or more further post-administration NRS score is 0 to 7.

357. The method of any preceding embodiment wherein the one or more further post-administration NRS score is reduced at least 1 point, at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline NRS score.

358. The method of any preceding embodiment wherein the one or more further post-administration NRS score is:

(c) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(d) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

359. The method of any preceding embodiment wherein determining the post-administration NRS score and/or the one or more further post-administration NRS score comprises the subject providing a numerical rating of their worst itch in the past 24 hours on a scale of 0 to 10, wherein "0" is no itch and "10" is the worst imaginable itch.

360. The method of any preceding embodiment wherein the post-administration NRS and/or further post-administration NRS is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS is:

(c) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(d) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

361. The method of any preceding embodiment wherein the post-administration NRS and/or further post-administration NRS is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS is:

(c) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(d) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

362. The method of any preceding embodiment wherein the post-administration NRS and/or further post-administration NRS is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration NRS and/or further post-administration NRS is:

(c) reduced at least 3 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8; or

(d) reduced at least 4 points relative to the baseline NRS score wherein the baseline NRS score is selected from the group consisting of at least 4, at least 5, at least 6, at least 7, at least 8, 6 to 9, and 7 to 8.

363. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the NRS score by at least 4 points after the third injection as a treatment dose.

364. The method of any preceding embodiment wherein the reduction in NRS score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

365. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline POEM (Patient-Orientated Eczema Measure) score.

366. The method of embodiment 365 wherein the determining a baseline POEM score comprises the subject providing a frequency rating for how often the following events have been caused by their eczema over the last week:

viii. Itchy skin,
ix. Disturbed sleep,.
x. Bleeding skin,
xi. Skin weeping or oozing clear fluid,
xii. Cracked skin,
xiii. Skin flaking off, and
xiv. Skin felt dry or rough.

367. The method of embodiment 366 wherein the frequency rating is selected from the group consisting of:

vi. "no days",
vii. ."1-2 days",
viii. "3-4 days",
ix. "5-6 days", and
x. "every day".

368. The method of embodiment 367 comprising

assigning a frequency rating score to each frequency rating, wherein "every day" is assigned a score of 4, "5-6 days" is assigned a score of 3, "3-4 days" is assigned a score of 2, "1-2 days" is assigned a score of 1 and "no days" is assigned a score of 0, and

adding together the frequency rating scores to calculate the POEM score.

369. The method of any one of embodiments 365 to 368, wherein a baseline POEM score of 0 to 2 indicates clear or almost clear eczema; a baseline POEM score of 3 to 7 indicates mild eczema; a baseline POEM score of 8 to 16 indicates moderate eczema; a baseline POEM score of 17 to 24 indicates severe eczema and a baseline POEM score of 25 to 28 indicates very severe eczema.

370. The method of any one of embodiments 365 to 369, wherein the baseline POEM score is selected from the group consisting of at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, 8 to 28, 8 to 24, 8 to 16, 17 to 24 and 25 to 28.

371. The method of any one of embodiments 365 to 370, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline POEM score is determined.

372. The method of any one of embodiments 365 to 371, further comprising determining the baseline POEM score.

373. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration POEM score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

374. The method of any preceding embodiment wherein the post-administration POEM score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

375. The method of any preceding embodiment wherein the post-administration POEM score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

376. The method of any preceding embodiment wherein the post-administration POEM score is determined at the end of the induction phase.

377. The method of any preceding embodiment wherein the post-administration POEM score is selected from the group consisting of 0 to 2; 3 to 7; 8 to 16; 17 to 24 and 25 to 28.

378. The method of any preceding embodiment wherein the post-administration POEM score is reduced at least 2 points, at least 3 points, at least 3.4 points, at least 4 points, at least 5

points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline POEM score.

379. The method of any preceding embodiment wherein the post-administration POEM score is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

380. The method of any preceding embodiment wherein the post-administration POEM score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline POEM score.

381. The method of any preceding embodiment wherein the post-administration POEM score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

382. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration POEM score.

383. The method of any preceding embodiment wherein the one or more further post-administration POEM score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

384. The method of any preceding embodiment wherein the one or more further post-administration POEM score is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

385. The method of any preceding embodiment wherein the one or more further post-administration POEM score is determined at the end of the induction phase.

386. The method of any preceding embodiment wherein the one or more further post-administration POEM score is selected from the group consisting of 0 to 2; 3 to 7; 8 to 16; 17 to 24 and 25 to 28.

387. The method of any preceding embodiment wherein the one or more further post-administration POEM score is reduced at least 2 points, at least 3 points, at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points or 10 points relative to the baseline POEM score.

388. The method of any preceding embodiment wherein the one or more further post-administration POEM score is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

389. The method of any preceding embodiment wherein determining the post-administration POEM score and/or the one or more further post-administration POEM score comprises the subject providing a frequency rating for how often the following events have been caused by their eczema over the last week:

viii. Itchy skin,
ix. Disturbed sleep,
x. Bleeding skin,
xi. Skin weeping or oozing clear fluid,
xii. Cracked skin,
xiii. Skin flaking off, and
xiv. Skin felt dry or rough.

390. The method of embodiment 389 wherein the frequency rating is selected from the group consisting of:

vi. "no days",
vii. "1-2 days",
viii. "3-4 days",
ix. "5-6 days", and
x. "every day".

391. The method of embodiment 390 comprising

assigning a frequency rating score to each frequency rating, wherein "every day" is assigned a score of 4, "5-6 days" is assigned a score of 3, "3-4 days" is assigned a score of 2, "1-2 days" is assigned a score of 1 and "no days" is assigned a score of 0, and

adding together the frequency rating scores to calculate the POEM score.

392. The method of any preceding embodiment wherein the post-administration POEM and/or further post-administration POEM is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

393. The method of any preceding embodiment wherein the post-administration POEM and/or further post-administration POEM is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

394. The method of any preceding embodiment wherein the post-administration POEM and/or further post-administration POEM is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration POEM and/or further post-administration POEM is reduced at least 2 points or at least 3 points relative to the baseline POEM score.

395. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the POEM score by at least 2 points after the third injection as a treatment dose.

396. The method of any preceding embodiment wherein the reduction in POEM score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a dose.

397. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline BSA (Body Surface Area) score.

398. The method of embodiment 397 wherein the determining a baseline BSA score comprises:

(a) Assigning a BSA value to each of the following body parts:

(j) Entire left arm,

(k) Entire right arm,

(l) Entire head,

(m) Entire chest,

(n) Entire abdomen,

(o) Entire back,

(p) Entire left leg,

(q) Entire right leg, and

(r) Groin,

(b) Estimating the proportion of each body part affected by atopic dermatitis,

(c) Multiplying the proportion of each body part affected by dermatitis by the BSA value for the body part to provide an affected BSA value for each body part, and

(d) Adding together the affected BSA values for the body parts to provide a BSA score.

399. The method of any one of embodiments 397 to 398, wherein the baseline BSA score is at least 10%, at least 15, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95%.

400. The method of any one of embodiments 397 to 399, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline BSA score is determined.

401. The method of any one of embodiments 397 to 400, further comprising determining the baseline BSA score.

402. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration BSA score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

403. The method of any preceding embodiment wherein the post-administration BSA score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

404. The method of any preceding embodiment wherein the post-administration BSA score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

405. The method of any preceding embodiment wherein the post-administration BSA score is determined at the end of the induction phase.

406. The method of any preceding embodiment wherein the post-administration BSA score is selected from the group consisting of less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%, less than 85%, less than 90% and less than 95%.

407. The method of any preceding embodiment wherein the post-administration BSA score is reduced at least 2 percentage points, at least 3 percentage points, at least 4 percentage points, at least 5 percentage points, at least 6 percentage points, at least 7 percentage points, at least 8 percentage points, at least 9 percentage points, 10 percentage points, at least 11 percentage points, at least 12 percentage points, at least 13 percentage points, at least 14 percentage points, at least 15 percentage points, at least 20 percentage points, at least 25 percentage points, at least 30 percentage points, at least 40 percentage points, at least 50 percentage points, at least 60 percentage points, at least 70 percentage points, at least 80 percentage points or at least 90 percentage points relative to the baseline BSA score.

408. The method of any preceding embodiment wherein the post-administration BSA score is reduced at least 5 percentage points relative to the baseline BSA score.

409. The method of any preceding embodiment wherein the post-administration BSA score is reduced at least 10 percentage points relative to the baseline BSA score, wherein the baseline BSA score is at least 10%.

410. The method of any preceding embodiment wherein the post-administration BSA score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline BSA score.

411. The method of any preceding embodiment wherein the post-administration BSA score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

412. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration BSA score.

413. The method of any preceding embodiment wherein the one or more further post-administration BSA score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

414. The method of any preceding embodiment wherein the one or more further post-administration BSA score is determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

415. The method of any preceding embodiment wherein the one or more further post-administration BSA score is determined at the end of the induction phase.

416. The method of any preceding embodiment wherein the one or more further post-administration BSA score is selected from the group consisting of less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%, less than 85%, less than 90% and less than 95%.

417. The method of any preceding embodiment wherein the one or more further post-administration BSA score is reduced at least 2 percentage points, at least 3 percentage points, at least 4 percentage points, at least 5 percentage points, at least 6 percentage points, at least 7 percentage points, at least 8 percentage points, at least 9 percentage points, 10 percentage points, at least 11 percentage points, at least 12 percentage points, at least 13 percentage points, at least 14 percentage

points, at least 15 percentage points, at least 20 percentage points, at least 25 percentage points, at least 30 percentage points, at least 40 percentage points, at least 50 percentage points, at least 60 percentage points, at least 70 percentage points, at least 80 percentage points or at least 90 percentage points relative to the baseline BSA score.

418. The method of any preceding embodiment wherein the one or more further post-administration BSA score is reduced at least 10 percentage points relative to the baseline BSA score.

419. The method of any preceding embodiment wherein determining the post-administration BSA score and/or the one or more further post-administration BSA score comprises:

(a) Assigning a BSA value to each of the following body parts:

(j) Entire left arm,

(k) Entire right arm,

(l) Entire head,

(m) Entire chest,

(n) Entire abdomen,

(o) Entire back,

(p) Entire left leg,

(q) Entire right leg, and

(r) Groin,

(b) Estimating the proportion of each body part affected by atopic dermatitis,

(c) Multiplying the proportion of each body part affected by dermatitis by the BSA value for the body part to provide an affected BSA value for each body part, and

(d) Adding together the affected BSA values for the body parts to provide a BSA score.

420. The method of any preceding embodiment wherein the post-administration BSA and/or further post-administration BSA is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration BSA and/or further post-administration BSA is reduced at least 10 percentage points relative to the baseline BSA score.

421. The method of any preceding embodiment wherein the post-administration BSA and/or further post-administration BSA is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration BSA and/or

further post-administration BSA is reduced at least 10 percentage points relative to the baseline BSA score.

422. The method of any preceding embodiment wherein the post-administration BSA and/or further post-administration BSA is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration BSA and/or further post-administration BSA is reduced at least 10 percentage points relative to the baseline BSA score.

423. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the BSA score by at least 10 percentage points after the third injection as a treatment dose.

424. The method of any preceding embodiment wherein the reduction in BSA score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

425. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline SCORAD (SCORing Atopic Dermatitis) index.

426. The method of embodiment 425 wherein the determining a baseline SCORAD index comprises:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) erythema,

(ii) edema/papulation,

(iii) oozing/crust,

(iv) excoriation,

(v) lichenification, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) puritis, and

(ii) sleep loss;

and

(d) Calculating the baseline SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

427. The method of embodiment 426 wherein determining the baseline SCORAD index comprises assigning to each clinical sign a sign intensity level selected from the group consisting of:

v. "absent"
vi. "mild"
vii. "moderate", and
viii. "severe".

428. The method of embodiment 427 comprising

assigning a sign intensity score to each sign intensity level, wherein "severe" is assigned a score of 3, "moderate" is assigned a score of 2, "mild" is assigned a score of 1 and "absent" is assigned a score of 0, and

adding together the sign intensity scores to calculate the intensity score "B".

429. The method of any one of embodiments 425 to 428 wherein determining the baseline SCORAD index comprises the subject or a caregiver providing a numerical rating of symptom severity for puritis and sleep loss in the past 3 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom.

430. The method of embodiment 429 comprising adding together the numerical ratings of symptom severity for puritis and sleep loss to calculate the severity score "C".

431. The method of any one of embodiments 425 to 430 wherein determining the baseline SCORAD index comprises calculating the baseline SCORAD index using the formula: SCORAD index = A/5 + 7B/2 + C.

432. The method of embodiment 425 to 431, wherein a baseline SCORAD index of 0 to 24 indicates mild disease; a baseline SCORAD index of 25 to 50 indicates moderate disease; and a baseline SCORAD index of 51 to 103 indicates severe disease.

433. The method of any one of embodiments 425 to 432, wherein the baseline SCORAD index is at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90 or at least 95.

434. The method of any one of embodiments 425 to 433, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline SCORAD index is determined.

435. The method of any one of embodiments 425 to 434, further comprising determining the baseline SCORAD index.

436. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration SCORAD index at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

437. The method of any preceding embodiment wherein the post-administration SCORAD index is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

438. The method of any preceding embodiment wherein the post-administration SCORAD index is determined at least around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

439. The method of any preceding embodiment wherein the post-administration SCORAD index is determined at the end of the induction phase.

440. The method of any preceding embodiment wherein the post-administration SCORAD index is selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95.

441. The method of any preceding embodiment wherein the post-administration SCORAD index is reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least

25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline SCORAD index.

442. The method of any preceding embodiment wherein the post-administration SCORAD index is reduced at least 20 points relative to the baseline SCORAD index.

443. The method of any preceding embodiment wherein the post-administration SCORAD index is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline SCORAD index.

444. The method of any preceding embodiment wherein the post-administration SCORAD index is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

445. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration SCORAD index.

446. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

447. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is determined at around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

448. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is determined at the end of the induction phase.

449. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95.

450. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline SCORAD index.

451. The method of any preceding embodiment wherein the one or more further post-administration SCORAD index is reduced at least 20 points relative to the baseline SCORAD index.

452. The method of any preceding embodiment wherein determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index comprises:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) erythema,

(ii) edema/papulation,

(iii) oozing/crust,

(iv) excoriation,

(v) lichenification, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) puritis, and

(ii) sleep loss;

and

(d) Calculating the SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

453. The method of any preceding embodiment wherein determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index comprises assigning to each clinical sign a sign intensity level selected from the group consisting of:

v. "absent"
vi. "mild"
vii. "moderate", and
viii. "severe".

454. The method of embodiment 453 comprising

assigning a sign intensity score to each sign intensity level, wherein "severe" is assigned a score of 3, "moderate" is assigned a score of 2, "mild" is assigned a score of 1 and "absent" is assigned a score of 0, and

adding together the sign intensity scores to calculate the intensity score "B".

455. The method of any preceding embodiment wherein determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index comprises the subject or a caregiver providing a numerical rating of symptom severity for puritis and sleep loss in the past 3 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom.

456. The method of embodiment 455 comprising adding together the numerical ratings of symptom severity for puritis and sleep loss to calculate the severity score "C".

457. The method of any preceding embodiment wherein determining the post-administration SCORAD index and/or the one or more further post-administration SCORAD index comprises calculating the SCORAD index using the formula: SCORAD index = A/5 + 7B/2 + C.

458. The method of any preceding embodiment wherein the post-administration SCORAD and/or further post-administration SCORAD is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD is reduced at least 20 points relative to the baseline SCORAD index.

459. The method of any preceding embodiment wherein the post-administration SCORAD and/or further post-administration SCORAD is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD is reduced at least 20 points relative to the baseline SCORAD index.

460. The method of any preceding embodiment wherein the post-administration SCORAD and/or further post-administration SCORAD is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration SCORAD and/or further post-administration SCORAD is reduced at least 20 points relative to the baseline SCORAD index.

461. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the SCORAD index by at least 20 points after the third injection as a treatment dose.

462. The method of any preceding embodiment wherein the reduction in SCORAD index is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

463. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline PO-SCORAD (Patient-Oriented SCORing Atopic Dermatitis) index.

464. The method of embodiment 463 wherein the determining a baseline PO-SCORAD index comprises:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) redness,

(ii) swelling,

(iii) oozing/scabs,

(iv) scratch marks,

(v) thickening of skin, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) itching, and

(ii) trouble sleeping

and

(d) Calculating the baseline PO-SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

465. The method of embodiment 464 wherein inputs for steps (a), (b) and (c) are provided by the subject or a caregiver.

466. The method of embodiment 465 wherein inputs for steps (a), (b) and (c) are inputted into a computer program via a graphical user interface by the subject or a caregiver.

467. The method of embodiment 466 wherein the estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A" is performed by a computer program.

468. The method of any one of embodiments 464 to 467 wherein determining the baseline PO-SCORAD index comprises the subject or a caregiver providing a sign intensity score for each clinical sign selected from the group consisting of:

i. "0"
ii. "1"
iii. "2", and
iv. "3";

wherein "0" is the lowest intensity and "3" is the highest intensity;

and wherein the sign intensity scores are added together to calculate the intensity score "B".

469. The method of embodiment 468 wherein the adding together of the sign intensity scores to calculate the intensity score "B" is performed by a computer program.

470. The method of any one of embodiments 463 to 469 wherein determining the baseline PO-SCORAD index comprises the subject or a caregiver providing a numerical rating of symptom

severity for itching and trouble sleeping in the past 2 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom.

471. The method of embodiment 470 comprising adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C".

472. The method of embodiment 471 wherein the adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C" is performed by a computer program.

473. The method of any one of embodiments 463 to 472 wherein determining the baseline PO-SCORAD index comprises calculating the baseline PO-SCORAD index using the the formula: PO-SCORAD index = A/5 + 7B/2 + C.

474. The method of any one of embodiments 463 to 473, wherein the baseline PO-SCORAD index is at least 25, at least 30, at least 35, at least 40, at least 45, at least 50, at least 55, at least 60, at least 65, at least 70, at least 75, at least 80, at least 85, at least 90 or at least 95.

475. The method of any one of embodiments 463 to 474, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline PO-SCORAD index is determined.

476. The method of any one of embodiments 463 to 475, further comprising determining the baseline PO-SCORAD index.

477. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration PO-SCORAD index at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

478. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

479. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

480. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is determined at the end of the induction phase.

481. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95.

482. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline PO-SCORAD index.

483. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is reduced at least 20 points relative to the baseline PO-SCORAD index.

484. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline PO-SCORAD index.

485. The method of any preceding embodiment wherein the post-administration PO-SCORAD index is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

486. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration PO-SCORAD index.

487. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

488. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

489. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is determined at the end of the induction phase.

490. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is selected from the group consisting of less than 10, less than 15, less than 20, less than 25, less than 30, less than 35, less than 40, less than 45, less than 50, less than 55, less than 60, less than 65, less than 70, less than 75, less than 80, less than 85, less than 90 and less than 95.

491. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is reduced at least 8 points, at least 8.7 points, at least 9 points, 10 points, at least 11 points, at least 12 points, at least 13 points, at least 14 points, at least 15 points, at least 20 points, at least 25 points, at least 30 points, at least 40 points, at least 50 points, at least 55 points, at least 60 points, at least 65 points, at least 70 points, at least 80 points or at least 90 points relative to the baseline PO-SCORAD index.

492. The method of any preceding embodiment wherein the one or more further post-administration PO-SCORAD index is reduced at least 20 points relative to the baseline PO-SCORAD index.

493. The method of any preceding embodiment wherein determining the post-administration PO-SCORAD index and/or the one or more further post-administration PO-SCORAD index comprises:

(a) Estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A",

(b) Assessing the intensity of the following clinical signs to provide an intensity score "B":

(i) redness,

(ii) swelling,

(iii) oozing/scabs,

(iv) scratch marks,

(v) thickening of skin, and

(vi) dryness;

(c) Assessing the severity of the following symptoms to provide a severity score "C":

(i) itching, and

(ii) trouble sleeping;

and

(d) Calculating the PO-SCORAD index using the extent score "A", the intensity score "B" and the severity score "C".

494. The method of embodiment 493 wherein inputs for steps (a), (b) and (c) are provided by the subject or a caregiver.

495. The method of embodiment 494 wherein inputs for steps (a), (b) and (c) are inputted into a computer program via a graphical user interface by the subject or a caregiver.

496. The method of embodiment 495 wherein the estimating the extent of the atopic dermatitis as a percentage of body area involvement to provide an extent score "A" is performed by a computer program.

497. The method of any one of embodiments 493 to 496 wherein determining the post-administration PO-SCORAD index comprises the subject or a caregiver providing a sign intensity score for each clinical sign selected from the group consisting of:

v. "0"

vi. "1"
vii. "2", and
viii. "3";

wherein "0" is the lowest intensity and "3" is the highest intensity;

and wherein the sign intensity scores are added together to calculate the intensity score "B".

498. The method of embodiment 497 wherein the adding together of the sign intensity scores to calculate the intensity score "B" is performed by a computer program.

499. The method of any preceding embodiment wherein determining the post-administration PO-SCORAD index comprises the subject or a caregiver providing a numerical rating of symptom severity for itching and trouble sleeping in the past 2 days and/or nights on a scale of 0 to 10, wherein "0" is no symptom and "10" is the worst imaginable symptom.

500. The method of embodiment 499 comprising adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C".

501. The method of embodiment 500 wherein the adding together the numerical ratings of symptom severity for itching and trouble sleeping to calculate the severity score "C" is performed by a computer program.

502. The method of any preceding embodiment wherein determining the post-administration PO-SCORAD index and/or the one or more further post-administration PO-SCORAD index comprises calculating the PO-SCORAD index using the formula: PO-SCORAD index = A/5 + 7B/2 + C.

503. The method of any preceding embodiment wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD is reduced at least 20 points relative to the baseline PO-SCORAD index.

504. The method of any preceding embodiment wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration

PO-SCORAD and/or further post-administration PO-SCORAD is reduced at least 20 points relative to the baseline PO-SCORAD index.

505. The method of any preceding embodiment wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration PO-SCORAD and/or further post-administration PO-SCORAD is reduced at least 20 points relative to the baseline PO-SCORAD index.

506. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the PO-SCORAD index by at least 20 points after the third injection as a treatment dose.

507. The method of any preceding embodiment wherein the reduction in PO-SCORAD index is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

508. The method of any preceding embodiment, wherein the atopic dermatitis has been assessed by determining a baseline DQLI (Dermatology Quality of Life Index) score.

509. The method of embodiment 508 wherein the determining a baseline DQLI score comprises the subject providing an answer for how much their skin problem has affected their life over the past week in the following areas:

xi. how itchy, sore, painful or stinging their skin has been,
xii. how embarrassed or self conscious they have been because of their skin,
xiii. how much their skin has interfered with them going shopping or looking after their home or garden,
xiv. how much their skin has influenced the clothes they wear,
xv. how much their skin has affected any social or leisure activities,
xvi. how much their skin has made it difficult to do any sport
xvii. whether their skin has prevented them from working or studying or if not how much their skin has been a problem at work or studying,
xviii. how much their skin has created problems with their partner of any of their close friends or relatives,
xix. how much their skin has caused any sexual difficulties
xx. how much of a problem has the treatment for their skin been.

510. The method of embodiment 509 wherein each answer is selected from the group consisting of:

vi. "Very much"
vii. "A lot"
viii. "A little"
ix. "Not at all"
x. "Not relevant"

511. The method of embodiment 510 comprising

assigning an answer score to each answer, wherein "very much" is assigned a score of 3, "a lot" is assigned a score of 2, "a little" is assigned a score of 1 and "not at all", "not relevant" or question unanswered are assigned a score of 0, and

adding together the answer scores to calculate a DQLI score.

512. The method of any one of embodiments 509 to 511, wherein the baseline DQLI score is selected from the group consisting of at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, 6 to 30, 6 to 10, 11 to 20, and 21 to 30.

513. The method of any one of embodiments 508 to 512, wherein a first injection of the anti-OX40L antibody or fragment thereof is administered on the same day as the baseline DQLI score is determined.

514. The method of any one of embodiments 508 to 513, further comprising determining the baseline DQLI score.

515. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining a post-administration DQLI score at least 7 days or at least 15 days after administering a first injection of the antibody or fragment thereof.

516. The method of any preceding embodiment wherein the post-administration DQLI score is determined at least around 7 days, at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

517. The method of any preceding embodiment wherein the post-administration DQLI score is determined at around 7 days, at around 15 days, around 29 days, around 57 days, around 85 days, around 113 days, around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

518. The method of any preceding embodiment wherein the post-administration DQLI score is determined at the end of the induction phase.

519. The method of any preceding embodiment wherein the post-administration DQLI score is selected from the group consisting of 0 to 1; 2 to 5; 6 to 10; 11 to 20; and 21 to 30.

520. The method of any preceding embodiment wherein the post-administration DQLI score is reduced at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 15 points or at least 20 points relative to the baseline DQLI score.

521. The method of any preceding embodiment wherein the post-administration DQLI score is reduced at least 2.2 points or at least 6.9 points relative to the baseline DQLI score.

522. The method of any preceding embodiment wherein the post-administration DQLI score is reduced at least 4 points relative to the baseline DQLI score.

523. The method of any preceding embodiment wherein the post-administration DQLI score is reduced at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85% or at least 90% relative to the baseline DQLI score.

524. The method of any preceding embodiment wherein the post-administration DQLI score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

525. The method of any preceding embodiment, further comprising assessing the atopic dermatitis by determining one or more further post-administration DQLI score.

526. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is determined at least around 15 days, at least around 29 days, at least around 57 days, at least around 85 days, at least around 113 days, at least around 169 days and/or at least around 253 days after administering a first injection of the antibody or fragment thereof.

527. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is determined at around 29 days, around 57 days, around 85 days, around 113 days , around 169 days and/or around 253 days after administering a first injection of the antibody or fragment thereof.

528. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is determined at the end of the induction phase.

529. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is selected from the group consisting of 0 to 1; 2 to 5; 6 to 10; 11 to 20; and 21 to 30.

530. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is reduced at least 4 points, at least 5 points, at least 6 points, at least 7 points, at least 8 points, at least 9 points, at least 10 points, at least 15 points or at least 20 points relative to the baseline DQLI score.

531. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is reduced at least 2.2 points or at least 6.9 points relative to the baseline DQLI score.

532. The method of any preceding embodiment wherein the one or more further post-administration DQLI score is reduced at least 4 points relative to the baseline DQLI score.

533. The method of any preceding embodiment wherein determining the post-administration DQLI score and/or the one or more further post-administration DQLI score comprises

the subject providing an answer for how much their skin problem has affected their life over the past week in the following areas:

xi. how itchy, sore, painful or stinging their skin has been,

xii. how embarrassed or self conscious they have been because of their skin,

xiii. how much their skin has interfered with them going shopping or looking after their home or garden,

xiv. how much their skin has influenced the clothes they wear,

xv. how much their skin has affected any social or leisure activities,

xvi. how much their skin has made it difficult to do any sport

xvii. whether their skin has prevented them from working or studying or if not how much their skin has been a problem at work or studying,

xviii. how much their skin has created problems with their partner of any of their close friends or relatives,

xix. how much their skin has caused any sexual difficulties

xx. how much of a problem has the treatment for their skin been.

534. The method of embodiment 533 wherein each answer is selected from the group consisting of:

vi. "Very much"

vii. "A lot"

viii. "A little"

ix. "Not at all"

x. "Not relevant"

535. The method of embodiment 534 comprising

assigning an answer score to each answer, wherein "very much" is assigned a score of 3, "a lot" is assigned a score of 2, "a little" is assigned a score of 1 and "not at all", "not relevant" or question unanswered are assigned a score of 0, and

adding together the answer scores to calculate a DQLI score.

536. The method of any preceding embodiment wherein the post-administration DQLI score and/or further post-administration DQLI score is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score is reduced at least 4 points relative to the baseline DQLI score.

537. The method of any preceding embodiment wherein the post-administration DQLI score and/or further post-administration DQLI score is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score is reduced at least 4 points relative to the baseline DQLI score.

538. The method of any preceding embodiment wherein the post-administration DQLI score and/or further post-administration DQLI score is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration DQLI score and/or further post-administration DQLI score is reduced at least 4 points relative to the baseline DQLI score.

539. The method of any preceding embodiment wherein the Atopic Dermatitis is treated as evidenced by a reduction in the DQLI score by at least 4 points after the third injection as a treatment dose.

540. The method of any preceding embodiment wherein the reduction in DQLI score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

541. A glass vial containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

542. A drug delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

543. A prefilled syringe containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment.

544. A microinfusor containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

545. A pen delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

546. The pen delivery device of embodiment 545 wherein the pen delivery device is a reusable pen delivery device.

547. The pen delivery device of embodiment 545 wherein the pen delivery device is a disposable pen delivery device.

548. An autoinjector delivery device containing a liquid formulation comprising an anti-OX40L antibody, or antigen-binding fragment thereof.

549. The glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device or autoinjector according to any one of embodiments 541 to 548 wherein the volume of the liquid formulation is up to 1 mL, up to 2 mL or up to 2.25 mL.

550. A kit comprising a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device or autoinjector according to any one of embodiments 541 to 548; and a label and/or instructions specifying administration in accordance with any one of embodiments 1 to 540.

551. A method according to any one of embodiments 1 to 540, wherein the antibody or fragment thereof is administered from a drug delivery device according to embodiment 542 or embodiment 549, a prefilled syringe according to embodiments 543 or embodiment 549, a microinfusor according to embodiment 544 or embodiment 549, a pen delivery device according to embodiment 546, embodiment 547 or embodiment 549 or an autoinjector delivery device according to embodiment 548 or embodiment 549.

552. A method according to any one of embodiments 1 to 540, wherein the antibody or fragment thereof is administered from a prefilled syringe according to embodiments 543 or embodiment 549.

553. An anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating Atopic Dermatitis in accordance with any one of embodiments 1 to 540.

554. A glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit according to any one of embodiments 541 to 550, for use in a method of treating Atopic Dermatitis in accordance with any one of embodiments 1 to 540 .

555. An anti-OX40L antibody, or antigen-binding fragment thereof, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit for use according to any one of embodiments 551 to 554 wherein the Atopic Dermatitis is Chronic Atopic Dermatitis.

556. The use of an anti-OX40L antibody, or antigen-binding fragment thereof, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with any one of embodiments 1 to 540.

557. The use of a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit according to any one of embodiments 541 to 550, for the manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with any one of embodiments 1 to 540.

558. The use of an anti-OX40L antibody, or antigen-binding fragment thereof, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit according to any one of embodiments 556 to 557 wherein the Atopic Dermatitis is Chronic Atopic Dermatitis.

559. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof specifically binds to human OX40L (hOX40L), optionally wherein the antibody blocks or neutralises the interaction between hOX40L and hOX40 receptor.

560. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof specifically binds to hOX40L with a K_D of from 1 nM to 0.01 nM, optionally wherein the specific binding is measured by surface plasmon resonance (SPR).

561. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof competes for binding to hOX40L with 02D10.

562. A method, glass vial, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof antagonises specific binding of hOX40L to OX40, optionally as determined using SPR or ELISA.

563. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof decreases IL-2 secretion by at least 50% (e.g., 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-2 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay.

564. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof decreases IL-13 secretion by at least 50% (e.g., 55%, 60%, 65% or 70%) as compared to IL-2 secretion in the absence of the anti-OX40L antibody or fragment, optionally wherein IL-13 secretion is measured in an allogenic mixed lymphocyte reaction (MLR) assay.

565. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody is a humanized, human or fully human antibody.

566. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the fragment is selected from the group consisting of multispecific antibodies (eg., bi-specific antibodies), intrabodies, single-chain Fv antibodies (scFv), camelized antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies single-chain antibodies, single domain antibodies, domain antibodies, Fv fragments, $F(ab')_2$ fragments, dimeric variable regions (diabodies), linear antibodies, and epitope-binding fragments thereof.

567. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises a HCDR3 of from 16 to 27 amino acids and derived from the recombination of a human VH gene segment, a human D gene segment and a human JH gene segment, wherein the human JH gene segment is IGHJ6 (e.g., IGHJ6*02).

568. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the HCDR3 of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46).

569. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the HCDR2 of antibody 2D10 (SEQ ID No:38 or SEQ ID No:44).

570. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the HCDR1 of antibody 2D10 (SEQ ID No:36 or SEQ ID No:42).

571. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the LCDR3 of antibody 2D10 (SEQ ID No:54 or SEQ ID No:60).

572. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the LCDR2 of antibody 2D10 (SEQ ID No:52 or SEQ ID No:58).

573. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the LCDR1 of antibody 2D10 (SEQ ID No:50 or SEQ ID No:56).

574. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises:

the CDRs of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3).

575. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRH1 sequence of the VH region of 2D10 as in SEQ ID No: 34.

576. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRH2 sequence of the VH region of 2D10 as in SEQ ID No: 34.

577. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRH3 sequence of the VH region of 2D10 as in SEQ ID No: 34.

578. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRL1 sequence of the VL region of 2D10 as in SEQ ID No: 48.

579. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRL2 sequence of the VL region of 2D10 as in SEQ ID No: 48.

580. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the CDRL3 sequence of the VL region of 2D10 as in SEQ ID No: 48.

581. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:

the VH and/or VL domains of antibody 2D10 (SEQ ID No:34 for VH and/or SEQ ID No:48 for VL).

582. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises an IgG4 constant region.

583. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises an IgG4 constant region comprising a Leu235Glu mutation and/or a Ser228Pro mutation according to the EU numbering system.

584. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody comprises an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128.

585. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises an IgG4-PE constant region having an amino acid sequence according to SEQ ID No:128; a VH domain having an amino acid sequence according to SEQ ID No:34 and a VL domain having an amino acid sequence according to SEQ ID No:48.

586. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the antibody or fragment thereof comprises a heavy chain having an amino acid sequence according to SEQ ID No:62 and a light chain having an amino acid sequence according to SEQ ID No:64.

587. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, for use in treating AD in a patient with a biomarker selected from the group consisting of IL-13, IL-22, and IL17A.

588. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, for use in treating AD in a patient having an elevated level of a biomarker selected from the group consisting of IL-13, IL-22, and IL17A.

589. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the subject is classified as a Th2 AD patient and/or a non-Th2 AD patient.

590. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to embodiment 589, wherein the subject classified as a non-Th2 AD patient has an elevated IL-22 and/or IL17A level.

591. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to embodiment 589 or 590, wherein the subject classified as a Th2 AD patient has an elevated IL-13 level.

592. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the method is a method for treating AD in a patient in need thereof, wherein the method comprises (a) measuring the level of a biomarker selected from the group consisting of IL-13, IL-22, and IL-17A in the biologic fluid

of the patient; (b) comparing the measured level with a reference level or threshold level; and (c) if the level of said biomarker is above the reference level or threshold level, administering to the patient the anti-OX40L antibody, or antigen-binding fragment thereof.

593. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the method comprises administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of the anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one biomarker selected from the group consisting of IL-13, IL-22, and IL-17A.

594. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding embodiment, wherein the method comprises an *in vitro* method for determining efficacy of a treatment of a subject having AD by administration of the anti-OX40L antibody, or antigen-binding fragment thereof, comprising determining *in vitro* a level of one or more biomarker selected from the group consisting of IL-13, IL-22 and IL-17A in a sample of said subject having AD, wherein said treatment is considered efficient if the level of IL-13, IL-22 and/or IL-17A is decreased.

595. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to embodiment 593 or 594, wherein the decrease is by day 1, 29, 113, 169, 253 or later in the subject following administration.

Definitions

The term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% (or 4%, or 3% or 2%, or, in an example, 1% or less) of a given value or range.

"Dose" refers to a quantity or amount of a medicine or drug taken or recommended to be taken at a particular time. As used herein, it is typically expressed in mg of the antibody or fragment thereof. It may alternatively be expressed in terms of mg/kg, accounting for patient bodyweight.

"Injection" refers to a means of administration and encompasses for example IV and subcutaneous injections. An IV injection may be referred to as an infusion. It is also used herein to refer to an instance of administration wherein that administration is by injection, for example in the phrase "one or more induction phase injections". Each injection will involve administration of a dose of antibody or fragment thereof.

"Disease modifying" refers to a long and sustained response or therapeutic effect. A skilled person knows how to recognize a long and sustained response or therapeutic effect. The response or

therapeutic effect may last longer than the presence of a therapeutically effective concentration of the antibody or fragment thereof in the body, such as in the skin. A long and sustained response or therapeutic effect may for instance be a response or therapeutic effect which persists after the last administration of the antibody or fragment thereof at least around seven half-lives, at least around eight half-lives, or at least around nine half-lives of the antibody or fragment thereof. A long and sustained response or therapeutic effect may for instance be a response or therapeutic effect which persists at least around six months, at least around seven months, at least around eight months or at least around nine months or longer after the last injection of the antibody or fragment thereof. A long and sustained response or therapeutic effect may be determined using any one of the methods of assigning disease severity disclosed herein, such as EASI (including EASI75 and EASI90) and IGA-AD. Disease modification may be apparent in an individual who has received drug and has achieved an IGA-AD of 0 or 1 for at least six months, optionally at least seven months, at least eight months or at least nine months. The disease modification (for example of at least six months) may begin at any suitable time after administration of the disease modifying drug. For example, the disease modification may begin at least 7 days or at least 15 days after administering the antibody or fragment thereof. The disease modification (for example of at least six months) may be during a period in which the subject is being treated, such as during an induction and/or maintenance phase as defined herein. The subject may receive a plurality (such as two, three, four, five, six, seven, eight, nine, ten etc) administrations of the antibody or fragment thereof during the at least six months during which an IGA-AD of 0 or 1 is maintained. When the drug treatment is stopped, the IGA-AD of 0 or 1 is maintained (i.e. is persistent) for at least a further 6 months, optionally at least a further seven months, at least a further eight months or at least a further nine months.

Cmin refers to the lowest concentration of the antibody or fragment thereof following administration and may also be termed the "trough concentration". Cmin may be measured between any two injections. Cmin (trough) values are typically the serum concentration in a sample obtained prior to drug administration on a day on which the subject is dosed. Cmin is therefore typically measured in a sample obtained on the day of a second (or a subsequent) injection of the antibody or fragment thereof, prior to injection of the antibody or fragment thereof. The sample may have been obtained within four hours before the injection of the antibody or fragment thereof. "Within four hours" may preferably refer to within three hours, within two hours, within one hour or within 45 minutes. The method may comprise measuring the serum concentration of the antibody or fragment thereof in one or more patient sample and determining Cmin, optionally further comprising obtaining the one or more patient sample.

Cmax refers to the peak concentration of the antibody or fragment thereof following administration. Cmax may be measured after a single injection or between any two injections. The calculated Cmax values are typically the highest drug serum concentration following each administration. This concentration may be measured in either an end-of-infusion blood sample (for

example at 45 mins, or other infusion period) or in some cases in the next nominal sampling point, for example at 4hrs after infusion. Typically, for an i.v. infusion the Cmax would usually occur at the end of infusion. Surprisingly, antibodies disclosed herein, in particular KY1005 may exhibit a Cmax which is delayed after the end of infusion (or delayed after injection). For example, Cmax may be at around 1 hour, 2 hours, 3 hours or 4 hours after the end of infusion (or after the injection). Cmin (trough) values are typically the serum concentration in a sample obtained prior to drug administration on a day on which the subject is dosed. Cmax is therefore typically measured in a sample obtained on the day of a first, a second (or a subsequent) injection of the antibody or fragment thereof, within four hours after injection or the start of the infusion of the antibody or fragment thereof. "Within four hours" may preferably refer to within three hours, within two hours, within one hour or within 45 minutes. The method may comprise measuring the serum concentration of the antibody or fragment thereof in one or more patient sample and determining Cmin, optionally further comprising obtaining the one or more patient sample.

Cmin and Cmax may be determined by measuring serum concentrations of an antibody or fragment thereof by any suitable known technique. As an example of a technique appropriate for measuring serum concentrations of an antibody or fragment thereof, concentrations of KY1005 in human serum were obtained using a validated chromogenic enzyme linked immunosorbent assay (ELISA) ligand binding assay that comprised a format of human OX40 ligand as capture antigen and a peroxidase labelled mouse anti-human IgG4 antibody as detector. The chosen format was considered to enable the measurement of free or active unbound KY1005 serum concentrations. The matrix KY1005 assay calibration curve ranged between 46.9 ng/mL (low limit of quantitation, LLOQ) and 1500 ng/mL. In pre-study validation, inter-assay imprecision (CV%) was ≤ 10.9% and inter-assay accuracy (% relative error) was ≤ 11.9%. Cmin and Cmax may be derived from modelling, using methods such as those described elsewhere herein.

The area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection may be determined by any suitable known technique. AUC0-inf represents the total drug exposure across time and may for example be used to indicate whether two formulations of the same dose result in equal amounts of tissue or serum exposure.

As used herein "induction phase" refers to a phase or period of treatment during which a therapeutic effect may be established. The induction phase can be of any suitable length and comprise one or more induction phase injections. Where a maintenance phase is also present, the induction phase precedes the maintenance phase.

As used herein, "induction phase injection" refers to an injection administered during the induction phase, including at the start of the induction phase and at the end of the induction phase.

As used herein, "induction dose" refers to the quantity or amount of the antibody or fragment thereof administered in an induction phase injection.

Das used herein, "maintenance phase" refers to a phase or period of treatment during which a previously established therapeutic effect may be maintained. The maintenance phase can be of any suitable length and comprise one or more maintenance phase injections. Where an induction phase is also present, the induction phase precedes the maintenance phase.

As used herein, "maintenance phase injection" refers to an injection administered during the maintenance phase, including at the start of the maintenance phase and at the end of the maintenance phase.

As used herein, "maintenance dose" refers to the quantity or amount of the antibody or fragment thereof administered in an maintenance phase injection.

As used herein, a "loading dose" refers to a higher dose administered prior to a subsequent lower dose.

As used herein "clinical response" refers to the outcome of a process to measure disease severity changes in response to a method of treatment. The clinical response may therefore be the outcome of any method which can be used to assign the severity of disease when assessing atopic dermatitis patients, including any of the methods of assigning disease severity described herein. The clinical response may be a post-administration score or index as described herein, such as a post-administration EASI score, post-administration IGA-AD score, post-administration NRS score or post-administration SCORAD index. The clinical response may be determined based on the experience of a clinician. The clinical response may be positive meaning there has been an improvement in the patient's AD following treatment. The clinical response may be negative meaning there has been no improvement, or a worsening of the patient's AD following treatment. A clinician may use a positive clinical response to transition a patient from an induction phase to a maintenance phase or to end treatment, for example. Alternatively, a negative clinical response may suggest the treatment has not yet been effective and should be continued, for example by prolonging the induction phase or the maintenance phase. A negative clinical response may also be used by a clinician to determine that treatment with the antibody or fragment thereof should cease.

As used herein a "treatment dose" refers to any administration of antibody or fragment thereof which comprises a therapeutically effective amount of antibody or fragment thereof. The term "treatment dose" is primarily used in the context of methods involving a loading dose, where the treatment dose is the dose or doses following the loading dose. The amount of antibody or fragment thereof in the loading dose may be defined relative to the treatment dose, for example the loading dose may have twice the amount of antibody or fragment thereof as the treatment dose. In some instances, the method may involve one or more treatment dose and one or more maintenance dose. The maintenance dose is defined as above. The maintenance dose may comprise the same amount of antibody or fragment thereof as the treatment dose. Alternatively, the maintenance dose may comprise a different amount of antibody or fragment thereof as the treatment dose. The dose interval between maintenance doses may be the same as the dose interval between treatment doses.

Alternatively, the dose interval between maintenance doses may be different to the dose interval between treatment doses. However, where the method comprises both a maintenance dose and a treatment dose, the maintenance dose is administered after the treatment dose. The term "treatment dose" may be used interchangeably with the term "induction dose" accordingly. Likewise, the time period during which treatment doses and a loading dose are being administered may be referred to as a "treatment phase" which is distinguishable from the "maintenance phase" and corresponds to the "induction phase" used elsewhere herein.

The amount of anti-OX40L antibody, or antigen-binding fragment thereof, administered to a subject according to the methods is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" may mean an amount of anti-OX40L antibody, or antigen-binding fragment thereof, that results in one or more of: (a) an improvement in one or more AD-associated parameters (as defined elsewhere herein); (b) an improvement and/or reduction in one or more AD-associated biomarkers; and/or (c) a detectable improvement in one or more symptoms or indicia of atopic dermatitis. A "therapeutically effective amount" also may include an amount of anti-OX40L antibody, or antigen-binding fragment thereof, that inhibits, prevents, lessens, or delays the progression of AD in a subject.

The term "C_{max}" refers to the maximum or peak concentration of an agent observed in a subject after its administration. "T_{max}" refers to the time it takes from dosing to reach C_{max}. With bolus intravenous administration, C_{max} is defined as occurring at the time of injection; therefore, T_{max} may be defined as zero.

The term "serum" is used herein in the context of pharmacokinetic measurements and derived parameters, however the term "plasma" (which further contains clotting factors) may be used interchangeably with the term "serum".

The term "absorption constant" or "ka" is the rate of absorption of a drug from its site of application through the body, and is typically only considered if the drug is administered by a route other than intravenous administration *(e.g.,* subcutaneous administration). If a drug is administered intravenously by single rapid injection, absorption is by-passed. The time for such injections is usually so short compared to other pharmacokinetic processes that it is customary, in one-compartment systems, to consider the peak serum (or plasma) concentration and the equilibrium distribution to occur simultaneously (see, e.g., Remington's Pharmaceutical Sciences, 16th Edition, Chapter 37. c. 1980 Mack Publishing Company).

The term "volume of distribution" or "Vd" is used to quantify the distribution of an administered drug. In a one compartment model, the body is assumed to behave as though it were a single compartment, that is, as if there were no barriers to the movement of drug within the total body space and the final equilibrium distribution is attained instantaneously. Vd is not necessarily the volume of the body or the total body water. The volume Vd is a fictive one considered to be equal to fD/C_p, where f is the fraction absorbed, D is the dose, and Cp is the serum (or plasma) concentration, in

which it is hypothetically assumed that the concentration is the same throughout the volume and is equal to the serum (or plasma) concentration. In reality, concentration is not homogenous throughout, but this cannot be determined from Cp alone (which simply averages all inputs and outputs); as long as distribution equilibrium is rapidly achieved, the kinetics as perceived through blood or urine concentrations are the same whether distribution is homogeneous or heterogeneous (see, e.g., Remington's Pharmaceutical Sciences, 16th 25 Edition, Chapter 37. c. 1980 Mack Publishing Company).

The "central compartment" or "Vc", is used to describe the first volume of distribution of a drug using a two-compartment model. In the two-compartment model, the body is considered to have two compartments in dynamic equilibrium. The compartment, into which the drug is directly absorbed and from which the drug eliminated, is called compartment 1 or the central compartment. The blood is a part of this compartment, is the transporting and distributing medium, and is the medium actually sampled for chemical and pharmacokinetic analysis (see, e.g., Remington's Pharmaceutical Sciences, 16th Edition, Chapter 37. c. 1980 Mack Publishing Company).

The term "Vp1", "Vp", "V_2", or "peripheral compartment" in a simple two-compartment model is closed and communicates with the environment only through the central compartment, being, as it were, peripheral to the events of absorption and elimination (see, e.g., Remington's Pharmaceutical Sciences, 16th Edition, Chapter 37. c. 1980 Mack Publishing Company).

The term "V_z" is the volume of distribution is used with single compartment models. Apparent V_z can be defined as V_z/F for subcutaneous administration.

The terms "Ve", "Vp", and "V_z" are fictive and defined by kinetic behaviour of the drug within the body and not necessarily by identifiable anatomical entities. The movement of drugs within and between compartments is defined e.g., by characteristic first-order rate constants, and the rate of movement of the drug from the first compartment to the second compartment, or in the reverse direction can be calculated in a manner similar to the rate of absorption (see, e.g., Remington's Pharmaceutical Sciences, 16th Edition, Chapter 37. c. 1980 Mack Publishing Company).

The term "Q" describes the rate in which a drug moves from or is cleared from the first compartment to the second compartment in a two-compartment model (intercompartmental clearance).

The term "CL", "rate of clearance" or "clearance" is the rate that a drug is eliminated from the serum (or plasma), typically substantially through the kidney and liver, however, other paths of elimination are also possible depending on the specific characteristics of the drug. CL may increase with increasing bodyweight, e.g., increases by approximately 10% per 10 kg change from greater than 75 kg to about 105 kg, and then increases approximately 7.5% when weight is greater than about 105 kg. CL may increase in the presence of ADA and neutralizing ADA, e.g., increases by about 30% in the presence of ADA and increases by about 66% in the presence of neutralizing ADA.

"Apparent clearance" can be defined as CL/F for subcutaneous administration.

The term "bioavailability" or "Fabs1" or "F%" or "F1" refers to a fraction or percent of a dose which is absorbed and enters the systemic circulation after administration of a given dosage form. The dose of the agent may be administered through any route, preferably, via intravenous or subcutaneous injection.

"Half life" or "t½" is the amount of time after administration of the drug for half of the dose to clear the subject.

"Area under the curve" or "AUC" is used to describe the serum concentration curve in single compartment pharmacokinetic calculations.

"Dupilumab" is a recombinant human monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling. Dupilumab is licensed for the treatment of adults and children aged 12-17 with moderate-to-severe atopic dermatitis (atopic eczema) who are possible candidates for systemic therapy. Dupilumab is described in WO2010053751 and EP2356151, both of which are hereby incorporated by reference in their entireties.

As used herein, "inadequate response" refers to a response that is not clinically sufficient.

As used herein, "intolerant to" refers to a treatment causing an undesirable clinical reaction in a patient, such as anaphylaxis.

As used herein, "refractory to" refers to an inadequate response in a patient who previously responded to treatment.

"Topical corticosteroid" refers to a type of steroid medicine applied directly to the skin to reduce inflammation and irritation. Steroids are a man-made version of hormones normally produced by the adrenal glands which are 2 small glands found above the kidneys. When taken in doses higher than the amount your body normally produces, steroids reduce redness and swelling (inflammation). This can help with inflammatory conditions such as asthma and eczema. Steroids also reduce the activity of the immune system, which is the body's natural defence against illness and infection.

"Conservative amino acid substitutions" result from replacing one amino acid with another having similar structural and/or chemical properties, such as the replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine. Thus, a "conservative substitution" of a particular amino acid sequence refers to substitution of those amino acids that are not critical for polypeptide activity or substitution of amino acids with other amino acids having similar properties (e.g., acidic, basic, positively or negatively charged, polar or non-polar, etc.) such that the substitution of even critical amino acids does not reduce the activity of the peptide, (i.e. the ability of the peptide to penetrate the blood brain barrier (BBB)). Conservative substitution tables providing functionally similar amino acids are well known in the art. For example, the following six groups each contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W). (See also Creighton, Proteins, W. H. Freeman and Company (1984),

incorporated by reference in its entirety.) In some embodiments, individual substitutions, deletions or additions that alter, add or delete a single amino acid or a small percentage of amino acids can also be considered "conservative substitutions" if the change does not reduce the activity of the peptide. Insertions or deletions are typically in the range of about 1 to 5 amino acids. The choice of conservative amino acids may be selected based on the location of the amino acid to be substituted in the peptide, for example if the amino acid is on the exterior of the peptide and expose to solvents, or on the interior and not exposed to solvents.

In alternative embodiments, one can select the amino acid which will substitute an existing amino acid based on the location of the existing amino acid, i.e. its exposure to solvents (i.e. if the amino acid is exposed to solvents or is present on the outer surface of the peptide or polypeptide as compared to internally localized amino acids not exposed to solvents). Selection of such conservative amino acid substitutions are well known in the art, for example as disclosed in Dordo *et al,* J. Mol Biol, 1999, 217, 721-739 and Taylor *et al.*, J. Theor. Biol. 119(1986);205-218 and S. French and B. Robson, J. Mol. Evol., 19(1983)171. Accordingly, one can select conservative amino acid substitutions suitable for amino acids on the exterior of a protein or peptide (i.e. amino acids exposed to a solvent), for example, but not limited to, the following substitutions can be used: substitution of Y with F, T with S or K, P with A, E with D or Q, N with D or G, R with K, G with N or A, T with S or K, D with N or E, I with L or V, F with Y, S with T or A, R with K, G with N or A, K with R, A with S, K or P.

In alternative embodiments, one can also select conservative amino acid substitutions encompassed suitable for amino acids on the interior of a protein or peptide, for example one can use suitable conservative substitutions for amino acids is on the interior of a protein or peptide (i.e. the amino acids are not exposed to a solvent), for example but not limited to, one can use the following conservative substitutions: where Y is substituted with F, T with A or S, I with L or V, W with Y, M with L, N with D, G with A, T with A or S, D with N, I with L or V, F with Y or L, S with A or T and A with S, G, T or V. In some embodiments, non-conservative amino acid substitutions are also encompassed within the term of variants.

As used herein an "antibody" refers to IgG, IgM, IgA, IgD or IgE molecules or antigen-specific antibody fragments thereof (including, but not limited to, a Fab, $F(ab')_2$, Fv, disulphide linked Fv, scFv, single domain antibody, closed conformation multispecific antibody, disulphide-linked scfv, diabody), whether derived from any species that naturally produces an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria. Antibodies can be humanized using routine technology.

As described herein, an "antigen" is a molecule that is bound by a binding site on an antibody agent. Typically, antigens are bound by antibody ligands and are capable of raising an antibody response *in vivo.* An antigen can be a polypeptide, protein, nucleic acid or other molecule or portion thereof. The term "antigenic determinant" refers to an epitope on the antigen recognized by an antigen-binding molecule, and more particularly, by the antigen-binding site of said molecule.

As used herein, the term "antibody fragment" refers to a polypeptide that includes at least one immunoglobulin variable domain or immunoglobulin variable domain sequence and which specifically binds a given antigen. An antibody fragment can comprise an antibody or a polypeptide comprising an antigen-binding domain of an antibody. In some embodiments, an antibody fragment can comprise a monoclonal antibody or a polypeptide comprising an antigen-binding domain of a monoclonal antibody. For example, an antibody can include a heavy (H) chain variable region (abbreviated herein as VH), and an OX40L (L) chain variable region (abbreviated herein as VL). In another example, an antibody includes two heavy (H) chain variable regions and two OX40L (L) chain variable regions. The term "antibody fragment" encompasses antigen-binding fragments of antibodies (e.g., single chain antibodies, Fab and sFab fragments, F(ab')2, Fd fragments, Fv fragments, scFv, and domain antibodies (dAb) fragments (see, e.g., de Wildt *et al.*, Eur J. Immunol., 1996; 26(3):629-39; which is incorporated by reference herein in its entirety)) as well as complete antibodies. An antibody can have the structural features of IgA, IgG, IgE, IgD, IgM (as well as subtypes and combinations thereof). Antibodies can be from any source, including mouse, rabbit, pig, rat, and primate (human and non-human primate) and primatized antibodies. Antibodies also include midibodies, humanized antibodies, chimeric antibodies, and the like.

As used herein, "antibody variable domain" refers to the portions of the OX40L and heavy chains of antibody molecules that include amino acid sequences of Complementarity Determining Regions (CDRs; i.e., CDR1, CDR2, and CDR3), and Framework Regions (FRs). VH refers to the variable domain of the heavy chain. VL refers to the variable domain of the Light chain. According to the methods used in this invention, the amino acid positions assigned to CDRs and FRs may be defined according to Kabat (Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991)) or according to IMGT nomenclature.

As used herein, the term "antibody binding site" refers to a polypeptide or domain that comprises one or more CDRs of an antibody and is capable of binding an antigen. For example, the polypeptide comprises a CDR3 (e.g., HCDR3). For example the polypeptide comprises CDRs 1 and 2 (e.g., HCDR1 and 2) or CDRs 1-3 of a variable domain of an antibody (e.g., HCDRs1-3). In an example, the antibody binding site is provided by a single variable domain (e.g., a VH or VL domain). In another example, the binding site comprises a VH/VL pair or two or more of such pairs.

As used herein, "OX40L antagonistic antibody" or "OX40L antagonist antibody" refers to an antibody or antigen-binding fragment thereof that is capable of inhibiting and/or neutralizing the biological signaling activity of OX40L, for example by blocking binding or substantially reducing binding of OX40 to OX40L.

As used herein, "genotyping" refers to a process of determining the specific allelic composition of a cell and/or subject at one or more position within the genome, e.g., by determining the nucleic acid sequence at that position. Genotyping refers to a nucleic acid analysis and/or analysis at the nucleic acid level. As used herein, "phenotyping" refers a process of determining the identity and/or

composition of an expression product of a cell and/or subject, e.g., by determining the polypeptide sequence of an expression product. Phenotyping refers to a protein analysis and/or analysis at the protein level.

As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment). For treatment to be effective a complete cure is not contemplated. The method can in certain aspects include cure as well.

As used herein, the term "pharmaceutical composition" refers to the active agent in combination with a pharmaceutically acceptable carrier e.g., a carrier commonly used in the pharmaceutical industry. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "administering," refers to the placement of a compound as disclosed herein into a subject by a method or route which results in at least partial delivery of the agent at a desired site. Pharmaceutical compositions comprising the compounds disclosed herein can be administered by any appropriate route which results in an effective treatment in the subject.

Multiple compositions can be administered separately or simultaneously. Separate administration refers to the two compositions being administered at different times, e.g., at least 10, 20, 30, or 10-60 minutes apart, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12 hours apart. One can also administer compositions at 24 hours apart, or even longer apart. Alternatively, two or more compositions can be administered simultaneously, e.g., less than 10 or less than 5 minutes apart. Compositions administered simultaneously can, in some aspects, be administered as a mixture, with or without similar or different time release mechanism for each of the components.

As used herein, "authorization number" or "marketing authorization number" refers to a number issued by a regulatory agency upon that agency determining that a particular medical product and/or composition may be marketed and/or offered for sale in the area under the agency's jurisdiction. As used herein "regulatory agency" refers to one of the agencies responsible for evaluating, e.g., the safety and efficacy of a medical product and/or composition and controlling the sales/marketing of such products and/or compositions in a given area. The Food and Drug Administration (FDA) in the US and the European Medicines Agency (EPA) in Europe are but two examples of such regulatory agencies. Other non-limiting examples can include SDA, MPA, MHPRA, IMA, ANMAT, Hong Kong Department of Health-Drug Office, CDSCO, Medsafe, and KFDA.

As used herein, "injection device" refers to a device that is designed for carrying out injections, an injection including the steps of temporarily fluidically coupling the injection device to a person's tissue, typically the subcutaneous tissue. An injection further includes administering an amount of liquid drug into the tissue and decoupling or removing the injection device from the tissue. In some embodiments, an injection device can be an intravenous device or IV device, which is a type of injection device used when the target tissue is the blood within the circulatory system, e.g., the blood in a vein. A common, but non-limiting example of an injection device is a needle and syringe.

As used herein, a "buffer" refers to a chemical agent that is able to absorb a certain quantity of acid or base without undergoing a strong variation in pH.

As used herein, "packaging" refers to how the components are organized and/or restrained into a unit fit for distribution and/or use. Packaging can include, e.g., boxes, bags, syringes, ampoules, vials, tubes, clamshell packaging, barriers and/or containers to maintain sterility, labeling, etc.

As used herein, "instructions" refers to a display of written, printed or graphic matter on the immediate container of an article, for example the written material displayed on a vial containing a pharmaceutically active agent, or details on the composition and use of a product of interest included in a kit containing a composition of interest. Instructions set forth the method of the treatment as contemplated to be administered or performed.

As used herein the term "comprising" or "comprises" is used in reference to antibodies, fragments, uses, compositions, methods, and respective component(s) thereof, that are essential to the method or composition, yet open to the inclusion of unspecified elements, whether essential or not.

The term "consisting of" refers to antibodies, fragments, uses, compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "e.g.," is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "e.g.," is synonymous with the term "for example."

Moderate-to-severe AD may also be considered to be present in patients who require frequent treatment with topical corticosteroids. A patient may also be said to have moderate-to-severe AD when the patient is resistant or refractory to treatment by either a topical corticosteroid or a calcineurin inhibitor or any other commonly used therapeutic agent known in the art. AD is a chronic inflammatory disease with recurrent symptoms often appearing as a rash on the skin. Signs and symptoms can include intense, persistent itching and skin dryness, cracking, redness, crusting and oozing.

As used herein a "diagnostic biomarker" is a biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

As used herein a "monitoring biomarker" is a biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

As used herein a "pharmacodynamic biomarker" is a biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent. The terms "pharmacodynamic biomarker" and "response biomarker" may be used interchangeably.

"IL-13" is expressed by Th2 cells, but also other cells (e.g., mast cells or ILC2s), and has been reported as one of the main drivers of Th2 responses in AD patients. IL-13 may be produced by Th2 cells. IL-13 may be described as a Th2 biomarker. As used herein "IL-13" may refer to a protein comprising IL-13, a fragment, sub-unit, or polypeptide sequence thereof.

"IL-22" is mainly produced by Th22 and Th17 cells, but also Th1 and other cell types, and signals through the IL22 receptor, which is expressed on tissue cells such as keratinocytes, but not on immune cells. IL-22 may be described as a non-Th2 biomarker. As used herein "IL-22" may refer to a protein comprising IL-22, a fragment, sub-unit, or polypeptide sequence thereof.

"IL-17A" is a cytokine produced by T-helper 17 cells. IL-17A plays important roles in allergic responses. IL-17A promotes inflammation by inducing various proinflammatory cytokines and chemokines, recruiting neutrophils, enhancing antibody production, and activating T cells. IL-17A is thought not to be produced by Th2 cells. IL-17A may be described as a non-Th2 biomarker. As used herein "IL-17A" may refer to a protein comprising IL-17A, a fragment, sub-unit, or polypeptide sequence thereof.

"IL-31" as a pruritogen is an important mediator of AD-associated itch. It is a Th2 cell-associated cytokine.

"IgE" is produced in response to parasitic infection but are also a hallmark of allergic reactions. High local and blood IgE levels are associated with allergic diseases such as asthma, allergic rhinitis and AD.

Some embodiments also include methods involving the use, quantification, and analysis of AD-associated biomarkers. As used herein, the term "AD-associated biomarker" means any biological response, cell type, parameter, protein, polypeptide, enzyme, enzyme activity, metabolite, nucleic acid, carbohydrate, or other biomolecule which is present or detectable in an AD patient at a level or amount that is different from (e.g., greater than or less than) the level or amount of the marker present or detectable in a non-AD patient. In some embodiments, the term "AD-associated biomarker" includes a biomarker associated with Type 2 helper T-cell (Th2)-driven inflammation. Exemplary AD-associated biomarkers include: IL-13, IL-22 and IL-17A. Certain embodiments of pertain to use of these biomarkers for monitoring disease reversal with the administration of an anti-OX40L antibody, or antigen-binding fragment thereof. Methods for detecting and/or quantifying such AD-associated biomarkers are known in the art; kits for measuring such AD-associated biomarkers are available from various commercial sources; and various commercial diagnostic laboratories offer services which provide measurements of such biomarkers as well.

As used herein, the terms "level" and "levels" can be used interchangeably with the terms "concentration" and "concentrations".

Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 19th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-19-0); Robert S. Porter et al. (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); Benjamin Lewin, Genes X, published by Jones & Bartlett Publishing, 2009 (ISBN-10: 0763766321); Kendrew *et al.* (eds.), Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Intersciences, Coligan et al., eds.

Unless otherwise stated, standard procedures were used, as described, for example in Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (4 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2012); Davis *et al.*, Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995); or Methods in Enzymology: Guide to Molecular Cloning Techniques Vol.152, S. L. Berger and A. R. Kimmel Eds., Academic Press Inc., San Diego, USA (1987); Current Protocols in Protein Science (CPPS) (John E. Coligan, *et al.*, ed., John Wiley and Sons, Inc.), Current Protocols in Cell Biology (CPCB) (Juan S. Bonifacino *et al.* ed., John Wiley and Sons, Inc.), and Culture of Animal Cells: A Manual of Basic Technique by R. Ian Freshney, Publisher: Wiley-Liss; 5th edition (2005), Animal Cell Culture Methods (Methods in Cell Biology, Vol. 57, Jennie P.

Mather and David Barnes editors, Academic Press, 1st edition, 1998) which are all incorporated by reference herein in their entireties.

Other terms are defined herein within the description of the various aspects of the invention.

All patents and other publications; including literature references, issued patents, published patent applications, and co-pending patent applications; cited throughout this application are expressly incorporated herein by reference for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with the technology described herein. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

The description of embodiments of the disclosure is not intended to be exhaustive or to limit the disclosure to the precise form disclosed. While specific embodiments of, and examples for, the disclosure are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the disclosure, as those skilled in the relevant art will recognize. For example, while method steps or functions are presented in a given order, alternative embodiments may perform functions in a different order, or functions may be performed substantially concurrently. The teachings of the disclosure provided herein can be applied to other procedures or methods as appropriate. The various embodiments described herein can be combined to provide further embodiments. Aspects of the disclosure can be modified, if necessary, to employ the compositions, functions and concepts of the above references and application to provide yet further embodiments of the disclosure. Moreover, due to biological functional equivalency considerations, some changes can be made in protein structure without affecting the biological or chemical action in kind or amount. These and other changes can be made to the disclosure in OX40L of the detailed description. All such modifications are intended to be included within the scope of the appended claims.

Specific elements of any of the foregoing embodiments can be combined or substituted for elements in other embodiments. Furthermore, while advantages associated with certain embodiments of the disclosure have been described in the context of these embodiments, other embodiments may also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages to fall within the scope of the disclosure.

It will be understood that particular configurations, concepts, aspects, examples, clauses and embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine study, numerous equivalents to the specific procedures described herein. Such

equivalents are considered to be within the scope of this invention and are covered by the claims. All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

Any part of this disclosure may be read in combination with any other part of the disclosure, unless otherwise apparent from the context.

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in OX40L of the present disclosure. While the compositions and methods have been described in terms of embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

Examples

Example 1. A Single and Multiple Ascending Dose, Placebo-controlled, Double-blind, Phase 1 Study to Evaluate the Safety and Tolerability of KY1005 in Healthy Volunteers, ClinicalTrials.gov Identifier: NCT03161288 (KY1005-CT01)

Study Design and Objectives

Male volunteers aged 18 to 45 years were recruited to a total of eight cohorts. In each cohort, KY1005 was administered by intravenous (IV) infusion over a period of 30 minutes to six volunteers, with two volunteers receiving placebo to match.

The primary objective of the study was to evaluate the safety and tolerability of KY1005. The secondary objective of the study was to evaluate the pharmacokinetics (PK) of KY1005 following single and repeat doses. Exploratory objectives were to evaluate the effect of KY1005 on dermal delayed type hypersensitivity (DTH) and humoral responses to immune challenges, immunophenotype and also to assess the immunogenicity of KY1005.

The overall study design is presented in **FIG. 1**. Healthy volunteers in Cohorts 1 to 3 received a single I.V. infusion of KY1005 (0.006, 0.018 or 0.05 mg/kg) or placebo, with blood samples taken up to Day 113. Cohorts 4 to 8 received an initial loading dose on Day 1 (0.15, 0.45, 1.35, 4.0 or 12 mg/kg), and two maintenance doses (50% of the loading dose), administered on Days 29 and 57.

Subjects were followed up to Day 113 (Cohorts 1 to 3) and Day 92 (Cohorts 4 to 8) and then discharged from the study.

Safety and tolerability

The primary objective of this study was to evaluate the safety and tolerability of KY1005. The following variables were assessed:

- Occurrence of AEs, SAEs and subject partner pregnancy up to Day 113 (Cohorts 1 to 3) and Day 92 (Cohorts 4 to 8).
- Changes in vital signs, laboratory safety data, anti-viral antibody levels and viral DNA, acute cytokines and ECGs.
- Changes in physical examination findings.

There were no SAEs and no pregnancies were reported in the partners of participating subjects.

Eight subjects were recruited to each of the eight cohorts. There were five withdrawals.

No AEs were judged to be severe. There were no reactions at the infusion site.

Physical examinations, vital signs, ECGs and laboratory safety data, including acute cytokines (evaluated in all cohorts) and markers of viral reactivation yielded no findings of concern. The hematology tests showed no evidence of an effect of treatment on the platelet count.

Pharmacokinetics

Serum concentrations of KY1005 were assessed using a validated enzyme-linked immunosorbent assay (ELISA) bioanalytical method. For Cohorts 1 to 3, serum concentrations of

KY1005 were assessed at the following time points: Days 1 to 3: pre- and at end of infusion, 4, 12, 24 and 48 hours after the end of infusion; Days 8, 11, 22, 29, 57, 85 and 113: single sample on each day. For Cohorts 4 to 8, serum concentrations of KY1005 were assessed at the following time points: Days 1 to 3: pre- and at end of infusion, 4, 12, 24 and 48 hours after the end of infusion; Days 8, 11, 22, 36, 64, 85 and 92: single sample on each day; Days 29 and 57: pre- and at end of infusion, 4, 12, 24 hours after the end of infusion.

The following PK measures were derived:

- C_{max} following the first, and, for Cohorts 4 to 8, second and third infusions.
- T_{max} following the first and, for Cohorts 4 to 8, second and third infusions.
- Trough concentrations (C_{min}) in Cohorts 4 to 8 following the first and second infusions and concentrations 28 days after the third infusion.
- Area under the serum concentration time curve (AUC) calculated using the linear trapezoidal method, including AUC from time zero to infinity (AUC_{inf}), AUC from time zero to time of last measurable concentration (AUC_{tlast}), AUC extrapolated from time (t) to infinity as a percentage of total AUC ($AUC_{\%extrapolated}$) and AUC during a dosage interval (AUC_I) following the first, and where relevant, second and third infusions.
- Apparent total body clearance of the drug from serum (CL).
- Apparent volume of distribution during terminal phase (Vz) and apparent volume of distribution at steady state (Vss).
- Apparent terminal half-life ($t_{1/2}$).

The profiles following single doses provided estimates of the PK measures following low (single) doses of KY1005 in Cohorts 1 to 3 as shown below (Table 3). These measures showed an increase in C_{max} that was proportional to dose. However, the CL was higher and the $t_{1/2}$ correspondingly shorter, particularly following the lowest dose (0.0177 L/h and 169.67 hours, respectively, for the dose of 0.006 mg/kg).

Table 3: Pharmacokinetics following a single dose (Cohorts 1 to 3)

	C_{max} (ng/mL) (geomean)	T_{max} (h) (median)	CL (L/h) (geomean)	Vz (L) (geomean)	$t_{1/2}$ (h) (average)
0.006 mg/kg, N = 6	133.14	0.53	0.0177	4.1579	169.67
0.018 mg/kg, N = 6	331.47	4.02	0.0146	6.4348	322.67
0.05 mg/kg, N	1260.27	2.25	0.0091	3.7463	289.83

CL = apparent total body clearance of the drug from serum; C_{max} = maximum observed serum concentration; CSR = clinical study report; geomean = geometric mean; NCA = non-compartmental analysis; $t_{1/2}$ = apparent terminal half-life; T_{max} = time to maximum observed serum concentration; V_z = apparent volume of distribution.

The dosing strategy of a loading/maintenance dose approximated steady state concentrations as shown by the C_{max} and C_{min} below (Table 4).

Table 4: Serum concentrations following loading and maintenance doses

Loading/ Maintenance dose (mg/kg)	C_{max} (ng/mL) / trough 1 (ng/mL) (geomean)	C_{max} (ng/mL) / trough 2 (ng/mL) (geomean)	C_{max} (ng/mL) / trough 3 (ng/mL) (geomean)
0.15/0.075 N = 6/6	3966.79 / 884.34	2803.32/ 995.72	2989.75 / 1149.80
0.45/0.225 N = 6/6	11762.33 / 2970.72	8079.09/ 2862.25	8595.40 / 3058.23
1.35/0.675 N = 6/6	33865.41 / 9611.21	25745.70/ 8828.21	28362.12 / 12802.80
4.0/2.0 N = 6/6	106503.19 / 25802.81	85508.52/ 30095.07	62765.34 / 31679.62
12/6.0 N = 6/5	286401.27 / 80667.81	228632.25/ 88400.59	247496.61 / 89074.93

C_{max} = maximum observed serum concentration; CSR = clinical study report; geomean = geometric mean; NCA = non-compartmental analysis.

Despite poor characterization of the terminal phase in the loading/maintenance dose cohorts (an inherent issue with repeat dosing), the PK measures following loading doses between 0.15 and 12 mg/kg (Cohorts 4 to 8) provided a useful insight. The elimination characteristics following the first dose in Cohorts 4 to 8 are shown below (Table 5).

Table 5: Pharmacokinetics following loading doses

Loading/ Maintenance dose (mg/kg)	CL (L/h) (geomean)	Vz (L) (geomean)	$t_{1/2}$ (h) (average)
0.15/0.075 N = 6	0.00666	4.65	498.2
0.45/0.225 N = 6	0.00596	4.64	554.5
1.35/0.675 N = 6	0.00561	4.16	557.1
4.0/2.0 N = 6	0.0067	4.63	486.4
12/6.0 N = 6	0.00701	5.4	545.4

CL = apparent total body clearance of the drug from serum; CSR = clinical study report; geomean = geometric mean; NCA = non-compartmental analysis; $t_{1/2}$ = apparent terminal half-life; V_z = apparent volume of distribution.

The $t_{1/2}$ estimates following these loading doses ranged between 486.4 and 557.1 hours (20 and 23 days), with no dose-related trend. A population PK analysis of the full data set provided a terminal half-life estimate of 38 days.

Immunogenicity and pharmacodynamic (PD) assessments

For evaluation of anti-KY1005 antibody response, serum titers of anti-KY1005 antibodies were assessed using a sensitive solid-phase extraction with acid dissociation (SPEAD) assay in blood samples pre-infusion and Days 11, 29, 57, 85 and 113 (or withdrawal) (Cohorts 1 to 3) or pre-first infusion and Days 11, 29 (pre-infusion), 57 (pre-infusion) and 92 (or withdrawal) (Cohorts 4 to 8).

Anti-KY1005 antibodies developed in some subjects who received KY1005 in Cohorts 1, 2, 3, 4, 5, 6 and 7 (Table 6), however, where ADAs were observed, no impact on PK was noted, suggesting weak or non-neutralizing antibody generation.

Table 6: Presence of anti-drug antibodies (FAS population)

Treatment	Protocol day	Negative	Positive	Missing
Cohorts 1 to 3, n (%)				
KY1005 0.006 mg/kg	0	5 (83)	1 (17)	0
	11	5 (83)	1 (17)	0
	29	5 (83)	1 (17)	0
	57	5 (83)	1 (17)	0
	85	5 (83)	1 (17)	0
	113	4 (67)	2 (33)	0
KY1005 0.018 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0
	29	5 (83)	1 (17)	0
	57	4 (67)	2 (33)	0
	85	4 (67)	2 (33)	0
	113	4 (67)	2 (33)	0
KY1005 0.05 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0
	29	5 (83)	1 (17)	0
	57	4 (67)	2 (33)	0
	85	3 (50)	3 (50)	0
	113	1 (17)	5 (83)	0
Placebo	0	6 (100)	0	0
	11	6 (100)	0	0
	29	6 (100)	0	0
	57	6 (100)	0	0
	85	5 (83)	0	1 (17)
	113	6 (100)	0	0
Cohorts 4 to 8				
KY1005 0.15 mg/kg	0	6 (100)	0	0
	11	5 (83)	1 (17)	0
	29	5 (83)	1 (17)	0
	57	5 (83)	1 (17)	0
	92	2 (33)	4 (67)	0
KY1005 0.45 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0

	29	6 (100)	0	0
	57	4 (67)	2 (33)	0
	92	4 (67)	2 (33)	0

Treatment	Protocol day	Negative	Positive	Missing
KY1005 1.35 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0
	29	6 (100)	0	0
	57	6 (100)	0	0
	92	5 (83)	1 (17)	0
KY1005 4 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0
	29	5 (83)	1 (17)	0
	57	5 (83)	1 (17)	0
	92	6 (100)	0	0
KY1005 12 mg/kg	0	6 (100)	0	0
	11	6 (100)	0	0
	29	6 (100)	0	0
	57	6 (100)	0	0
	92	6 (100)	0	0
Placebo	0	10 (100)	0	0
	1	1 (100)	0	0
	11	10 (100)	0	0
	29	10 (100)	0	0
	57	9 (90)	0	1 (10)
	92	9 (100)	0	0

FAS = Full Analysis Set

PD assessments demonstrated that KY1005 is a pharmacologically active compound in inhibiting the neo-antigen response and blunting the DTH skin changes. (see "KY1005 a novel anti-OX40L mAb with potential in atopic dermatitis (AD): Results of a Phase 1 study assessing the safety, pharmacokinetics, and T-cell-dependent antibody response (TDAR) in healthy volunteers", M. Saghari, *et al*, 24th World Congress of Dermatology, Milan, June 10-15, 2019 and "OX40L blocking monoclonal antibody KY1005 strongly suppresses the delayed-type hypersensitivity skin response to KLH in healthy volunteers", M. Saghari, *et al*, 24th World Congress of Dermatology, Milan, June 10-15, 2019)

As shown **FIG. 2A-B**, immunization with recall antigen, tetanus toxoid (TT), resulted in a humoral (IgM and IgG) response in all who were immunized. No observable effect of KY1005 on mean anti-TT IgG levels (**FIG. 2A**) were observed although anti-TT IgM (**FIG. 2B**) suppression was numerically greater than placebo in all treatment arms but not dose dependent.

Conclusions

KY1005 was studied in healthy volunteers in eight cohorts across a dose range. There was no evidence for cytokine release, reduction in platelet counts or predisposition to infection.

PK evaluation revealed a consistent dose-proportional C_{max} and C_{min}. KY1005 was cleared slowly and the serum concentrations at 4 and 12 hours were very similar to those at the end-of-infusion. The elimination characteristics suggested a more rapid clearance at lower doses. This may have been caused by OX40L-mediated clearance dominating at lower doses. At higher doses, clearance appeared to be independent of dose and unaffected on repeat dosing. The $t_{1/2}$ based on the loading doses ranged between 20 and 23 days, while a population PK analysis of the full data set provided a terminal half-life estimate of 38 days (99), so the first C_{max} was greater than the maintenance dose C_{max}. However, C_{max} and C_{min} on this dosing strategy provided acceptable exposure throughout the dosing interval.

Anti-drug antibodies were detected in a minority of subjects. The PK of KY1005 did not appear to be affected in those subjects who reacted, suggesting weak or non-neutralizing antibody generation.

The PD assessments showed an immunomodulatory effect in response to neo-antigen exposure, statistically significant at some dose regimes, for the DTH skin assessment. The results of downregulation of antibody responses to neo-antigen challenge were less clear than for DTH but provided additional evidence of relevant pharmacological activity. Suppression of the T-cell dependent antibody response (TDAR) against a neo-antigen (KLH subunit) was observed above the lowest dose of KY1005 (0.15 mg/kg). The suppression in the IgG response was more marked than the IgM response. TDAR against recall antigen (TT) highlighted no observable effect of KY1005 on anti-TT IgG although anti-TT IgM suppression was numerically greater than placebo in all treatment arms but not dose dependent.

As is usual in these kinds of assessments, there was no clear dose-response relationship, although there is some indication that KY1005 was more effective in cohorts dosed at 0.45 mg/kg and above, with the most pronounced response being observed in the 12 mg/kg cohort. Based on these PD assessments, it can be concluded that KY1005 is a pharmacologically active compound in inhibiting the neo-antigen response and blunting the DTH skin changes.

Example 2. A Phase IIa, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multicenter Study of An Anti-Ox40L Monoclonal Antibody (KY1005) In Moderate To Severe Atopic Dermatitis, ClinicalTrials.gov Identifier: NCT03754309 (KY1005-CT02)

Primary Objective

The primary objective of the study was to explore the efficacy and safety of two regimes of KY1005 on the signs of AD using the Eczema Area and Severity Index (EASI) and the incidence of treatment-emergent adverse events (TEAEs).

Secondary Objectives

- To explore the effect of two regimes of KY1005 on changes in EASI over time.
- To characterize the pharmacodynamic (PD) response to KY1005

Additional Objectives

- To explore the effect of two regimes of KY1005 on additional physician assessments of AD activity/severity (EASI 50, EASI 75, EASI 90, validated Investigator Global Assessment (vIGA), SCORing of Atopic Dermatitis (SCORAD) Index and affected body surface area (BSA))
- To explore the effect of two regimes of KY1005 on patient-reported AD activity/severity (Patient Oriented Eczema Measure (POEM), Patient Oriented (PO) SCORAD, Dermatology Quality of Life Index (DLQI) and Numerical Rating Scale (NRS) for pruritus)
- To characterize the PK of KY1005
- To characterize the PD response of KY1005 including the anti-KY1005 antibody response
- To explore the durability of clinical response and safety up to 253 days from Baseline in patients who were defined as responders at Day 113;
- To characterize the PD response to KY1005

Primary Endpoints

- Percentage change in EASI from Baseline to Day 113
- Incidence of TEAEs

Additional Endpoints

- Percentage and absolute change from Baseline in EASI over time (Also analyzed for the responder group)
- Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI 50) at Days 15, 29, 57, 85 and 113 (Also analyzed for the responder group)
- Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 15, 29, 57, 85 and 113 (Also analyzed for the responder group)
- Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI 90) at Days 15, 29, 57, 85 and 113 (Also analyzed for the responder group)
- Percentage of patients with a response of vIGA 0 or 1 at Day 113 and over time (Also analyzed for the responder group)

- Change in affected BSA from Baseline to Day 113 and over time (Also analyzed for the responder group)
- Change in vIGA, SCORAD Index, POEM, PO-SCORAD, DLQI and NRS from Baseline to Day 113 and over time (Also analyzed for the responder group)
- For each patient (receiving KY1005) and for both KY1005 regimes:
    - Maximum observed serum concentration (C_{max}) following the first and fourth (third maintenance) infusions. Peak concentrations (end of infusion) following all infusions
    - Time to maximum observed serum concentration (t_{max}) following the first and fourth infusions
    - Trough concentration (C_{min}) following the first, second and third infusions and the concentration 28 days after the fourth infusion
    - Area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) and fourth (AUC in the dosing interval [AUC_{0-28}]) infusions
    - Estimates of clearance (CL), apparent volume of distribution (Vd) and $t_{1/2}$
- Anti-KY1005 antibody titer and number of patients with positive response (Also analyzed for the responder group)

Study Design

This was a phase IIa, randomized, double-blind, placebo-controlled, parallel group, multicenter study to explore the efficacy and safety of KY1005 in adult patients with moderate to severe AD who had a documented history, within 6 months prior to baseline, of either inadequate response to topical treatments or inadvisability of topical treatments. Approximately 84 patients aged 18 to 75 years were to be enrolled in the study with a study duration of up to 28 days for screening and then up to Day 113 for all patients in the main study. The overall study design is depicted in **FIG. 3**.

After providing informed consent, patients were assessed for study eligibility at the screening visit, which was completed within 28 days prior to randomization. During the Screening period, treatments for AD were washed out for at least 14 days prior to baseline (except bland moisturizers). Patients were required to apply bland moisturizers (emollients) with no additives (e.g., urea) at least twice daily for at least the 7 consecutive days before baseline and continued throughout the study.

Patients who continued to meet eligibility criteria at Baseline underwent Day 1/Baseline assessments and were randomized in a 1:1:1 ratio to receive an I.V. injection of KY1005 at a low (200 mg) or high (500 mg) dose, followed by three maintenance doses at 50% of the loading dose at 28-day intervals on Days 29, 57 and 85, or matching placebo.

Efficacy, safety, PK and PD assessments were performed at clinic or telephone visits at 7-day intervals from Day 1 through Day 113 (main study). To explore the safety and durability of effect for up to 253 days from baseline, all patients continued in the study extension (to Day 253 (Visit 23)), with assessments up to the time that they relapsed or commenced drugs that have significant impact on AD. Patients who had responded (vIGA 0/1) at Day 113 (Visit 18) assessment were required to continue with all assessments. Patients who did not respond (vIGA 2-4) were assessed for safety only.

The primary analysis occurred once all patients had completed Day 113 (or earlier/withdrawal). It was planned that patients would be discharged from this study no later than 253 days after administration of the loading dose.

Inclusion Criteria

1. Adults (≥18 years but <75 years of age) with AD for 1 year or longer at Baseline (Day 1; prior to first administration of treatment).
2. EASI of 12 or higher at the Screening Visit and 16 or higher at Baseline.
3. vIGA of 3 or 4 at Baseline.
4. AD involvement of 10% or more of BSA at Baseline.
5. Documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments.
6. Must have applied a stable dose of topical bland emollient (simple moisturiser, no additives [e.g., urea]) at least twice daily for at least 7 consecutive days before Baseline.

Exclusion Criteria

1. Treatment with any of the following prior to first KY1005 administration (Baseline):
   - Systemic corticosteroids and tacrolimus within 4 weeks
   - Systemic cyclosporin A within 3 weeks
   - Other systemic immunosuppressive or immunomodulatory drugs (including leukotriene inhibitors) within 3 months
   - Topical corticosteroids, tacrolimus or pimecrolimus, within 2 weeks
   - Prescription or non-prescription moisturisers with additives (e.g., urea, filaggrin) within 2 weeks
   - Phototherapy or allergen immunotherapy within 4 weeks
   - Dupilumab within 3 months
   - Investigational therapy for the treatment of other conditions within 5 half-lives or the limit of PD effects or 3 months where the apparent terminal half-life ($t_{1/2}$) is not known
2. Weight <40 kg or >120 kg at baseline

(Other Inclusion and Exclusion Criteria available online at ClinicalTrials.gov, Identifier: NCT03754309)

Treatments Administered

All patients received a total of four I.V. infusions. For patients randomized to KY1005, patients in the high and low dose groups received a loading dose of 500 mg and 200 mg KY1005, respectively, on Day 1, followed by three maintenance doses at 50% of the loading dose at 28-day intervals on Days 29, 57 and 85. Patients randomized to the placebo group received four infusions of matching placebo on Days 1, 29, 57 and 85.

Identity of Investigational Product(s)

KY1005 and matching placebo were presented as colourless or slightly yellow, clear to slightly opalescent sterile solutions filled to a nominal 10 mL volume in a 10 mL clear glass vial for I.V. administration from an infusion bag.

KY1005 was formulated at a concentration of 10 mg/mL.

The matching placebo contained identical components but without KY1005 and was also used to dilute KY1005 to the correct dose concentration in a fixed volume to maintain blinding.

The bulk supplies of drug and prepared doses were stored at 2°C to 8°C. Prepared doses were to be used within 28 hours of preparation. The maximum period of storage at 2°C to 8°C was the first 24 hours; doses were then to be brought to room temperature for no more than four hours, prior to administration

Selection of Doses in the Study

A healthy volunteer study (as described in Example 1 above, KY1005-CT01) was conducted in which the repeat dose part involved a dosing strategy (loading/maintenance) comparable to the regime proposed for this study. The volunteers received an initial loading dose (0.15, 0.45, 1.35, 4.0 or 12 mg/kg) and two maintenance doses at 50% of the loading dose (0.075, 0.225, 0.675, 2.0 or 6.0 mg/kg, respectively), administered at 28-day intervals.

The PK evaluation revealed a consistent dose-proportional C_{max} and C_{min}, with t_{max} most often occurring at the end-of-infusion. At doses that encompassed the proposed 100 to 500 mg flat dose, CL was independent of dose and unaffected on repeat dosing. The healthy volunteer study involved dosing once every 28 days. Peak and trough concentrations on this strategy provided acceptable exposure throughout the dosing interval.

The PD assessments showed an immunomodulatory effect of KY1005 although there was no clear dose-response relationship. However, there was some indication that 0.15 mg/kg followed by two doses of 0.075 mg/kg was placebo-like in terms of the immunomodulatory effect. A pharmacological effect (as assessed by KLH TDAR and DTH) was seen at the higher dose regimes 0.45/0.225, 1.35/0.675, 4.0/2.0 and 12/6.0 mg/kg.

The two active treatment regimes in this study represent a more than two-fold difference in exposure in a range that has been shown to have PD effects on delayed type hypersensitivity immune challenge to the skin in healthy volunteers. The I.V. route facilitated the administration of the proposed doses in a blinded design.

Selection and Timing of Dose for Each Patient

Patients received KY1005 low dose (flat dose of 200 mg [loading dose]/100 mg [maintenance dose]), KY1005 high dose (flat dose of 500 mg [loading dose]/250 mg [maintenance dose]) or matching placebo (**FIG. 3**). The loading dose of KY1005 was followed 28 days later by three maintenance doses each given at further 28-day intervals. A loading dose followed by maintenance doses was expected to achieve steady state more rapidly in the target tissues, potentially allowing an earlier onset of effect.

Efficacy Assessments

The efficacy of KY1005 in the treatment of AD was assessed using change in EASI, vIGA, SCORAD Index and affected BSA. Investigator-performed assessments were carried out by the same assessor on each occasion for an individual patient. Patient-reported outcomes were assessed using the POEM, DLQI, PO-SCORAD Index and the NRS for pruritus. The POEM, PO-SCORAD, DLQI and NRS for pruritus were recorded by the patient using an internet-enabled device in their local language.

Eczema Area Severity Index

The EASI is an Investigator-assessed validated tool used to measure the extent (area) and severity of AD (Hanifin JM, *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis: EASI: assessment of reliability in AD. Exp Dermatol., 2001 Feb;10(1):11–8.)

The Investigator assessed the severity of four disease characteristics (erythema (E), induration/papulation (I), excoriation (X) and lichenification (L)) on a scale of zero (absent) to 3 (severe). In addition, the extent of involvement of four body sites (head/neck, trunk, upper extremities and lower extremities) was assessed as a percentage of BSA (Area Score) and then converted to a score of zero (none in that region) to 6 (>90% to 100% of the entire region affected.)

For each major section of the body (head, upper extremities, trunk and lower extremities), EASI score = (E+I+X+L)×Area Score. The total EASI score was the weighted total of the section EASI using the weights 10% (head), 20% (upper extremities), 30% (trunk) and 40% (lower extremities). The minimum possible EASI score was zero and the maximum possible EASI score was 72, where a higher score indicates increased extent and severity of AD.

Validated Investigator Global Assessment

The vIGA is a validated Investigator-lead assessment scale used to determine severity of AD and clinical response to treatment. As shown in Table 7, it is based on a 5-point scale, ranging from 0 (clear) to 4 (severe).

Table 7: Validated Investigator Global Assessment

Score	Morphological description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

SCORing of Atopic Dermatitis (SCORAD) Index

The SCORAD Index is a validated clinical tool that was developed to standardize the evaluation of the extent and severity of AD (Severity Scoring of Atopic Dermatitis: The SCORAD Index. Dermatology. 1993;186(1):23–31.)

To determine the extent of AD, the affected area (A) as a percentage of the whole body was determined, with a maximum score of 100% (head and neck (9%), upper limbs (9% each), lower limbs (18% each), anterior trunk (18%), back (18%), genitals (1%). The severity (B) of six specific symptoms of AD (redness, swelling, oozing/crusting, scratch marks, skin thickening [lichenification],

dryness [area where there was no inflammation]) was assessed on a 4-point scale, with a maximum score of 18: none (0), mild (1), moderate (2) or severe (3). Subjective symptoms (i.e., itch and sleeplessness; C) were recorded as scored by the patient or relative on a visual analogue scale, where 0 was no itch (or sleeplessness) and 10 was the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. The SCORAD score for each patient was calculated as: A/5 + 7B/2 + C.

Body Surface Area (BSA) Involvement of Atopic Dermatitis

The BSA affected by AD was assessed for each major section of the body (head, trunk, upper extremities and lower extremities) and was reported as a percentage of the total from each body section. The total BSA involvement was derived from the sum of each body section.

Patient Oriented Eczema Measure (POEM)

The POEM is a tool used for monitoring atopic eczema severity. It focuses on the illness as experienced by the patient and was completed using an internet-enabled device. The questionnaire consisted of seven questions pertaining to the symptoms of AD and their frequency. Scores were based on a scale of zero (no days) to 4 (every day in the last week) for each question, with a maximum score of 28 possible for all questions. A POEM total score was correlated to eczema severity (0-2 [clear or almost clear], 3-7 [mild], 8-16 [moderate], 17-24 [severe], 25-28 [very severe].)

Patient Oriented – SCORing of Atopic Dermatitis Index (PO-SCORAD)

The PO-SCORAD Index is a validated self-assessment score that allows the patient to comprehensively evaluate the actual course of AD, using subjective and objective criteria derived mainly from the SCORAD Index (Stalder J-F, *et al.*, Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe: PO-SCORAD self-assessment scale validation, Allergy, 2011 Aug;66(8):1114–21.) An internet-enabled device was used to complete the PO-SCORAD Index. The total PO-SCORAD score was calculated as the sum of the surface area score, intensity score and subjective symptom score, and was interpreted as mild (<20), moderate (≥20 to ≤40) and severe (>40).

Dermatology Quality of Life (QoL) Index (DLQI)

The DLQI is a dermatology-specific QoL instrument and is a simple, validated questionnaire. The instrument consists of ten questions pertaining to the effect of AD on QoL. Scores were based on a scale of zero (not at all/not relevant/question unanswered) to 3 (very much/prevented work or studying), with a maximum score of 30 possible for all questions. The total score was correlated to

the detrimental effect of AD on QoL (0-1 [no effect at all on patient's life], 2-5 [small effect], 6-10 [moderate effect], 11-20 [very large effect] and 21-30 [extremely large effect].)

Numerical Rating Scale (NRS) for Pruritus

The NRS for pruritus is an assessment tool that was used to assess the patient's worst itch as a result of their AD in the previous 24 hours. This was recorded daily, ideally in the morning, using an internet-enabled device with patients asked, "On a scale of "0" (no itch) to "10" (worst imaginable itch), how was your worst itch in the past 24 hours?"

Pharmacokinetic Assessments

Serum concentrations of KY1005 were assessed in blood samples taken during the study using a validated ELISA bioanalytical method.

At least two samples for serum concentration of KY1005 were withdrawn on infusion days. Samples for serum concentration of KY1005 were also withdrawn on non-infusion days.

Samples were analyzed, unblinded

Pharmacokinetic Parameter Derivation

In the main study, the following PK values were derived for each patient (receiving KY1005) and for both KY1005 regimes. In the study extension, the following PK values were determined from individual concentration-time data of KY1005 in serum for both KY1005 treatment groups by non-compartmental analysis using the actual, exact blood sampling times based on the PK Population:

- C_{max} following the first and fourth (third maintenance) infusions.
- t_{max} following the first and fourth infusions.
- C_{min} following the first, second, third and fourth infusions.
- Concentration of KY1005 45 minutes after the start of all infusions ('peak concentrations').
- $AUC_{0\text{-}28}$ following the first and fourth infusions.
- $AUC_{0\text{-}inf}$ following the first and fourth infusions.
- AUC percentage extrapolated area ($AUC_{extrap[\%]}$) following the first and fourth infusion.
- Terminal rate constant (λz) following the first infusion
- $t_{1/2}$ following the first and fourth infusions
- CL (mL/day) for the fourth infusion.
- Vd (L) for the fourth infusion.
- λz for the fourth infusion.
- Average concentration after the fourth infusion.

- Fluctuation (%) after the fourth infusion.
- Expected accumulation index after the fourth infusion.

Blood Samples for Assessment of Serum Anti-Drug Antibodies

Serum titers of anti-KY1005 antibodies were assessed in blood samples taken during the study using a validated semi-quantitative ECLIA bioanalytical method. Samples were analyzed, unblinded.

Disposition of Patients

A total of 89 patients were randomized in the study, comprising 29, 30 and 30 patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively. One patient in the placebo group terminated the study early due to a protocol deviation and did not receive study treatment. Of the 88 treated patients, 20 (69.0%), 22 (73.3%) and 17 (58.6%), respectively, completed the main study (up to Day 113). Three patients terminated the study early due to AEs, all of whom were in the placebo group. The remaining reasons for early termination were withdrawal of consent (six, five and three patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively), 'Other' reasons (two, three and five patients, respectively) pertaining to issues with data from Site 216 and failure to meet randomization criteria (one patient in the KY1005 low dose group). Overall, 17 (58.6%), 19 (63.3%) and 14 (48.3%) patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively, completed the study extension (up to Day 253).

Baseline Disease Characteristics

Disease characteristics at Baseline are summarized for the FAS in Table 8. Baseline disease characteristics were as expected for a population of patients with moderate to severe AD and were generally well matched across the treatment groups. The number of patients in the FAS with a vIGA score of 4 (severe) was higher in the placebo group (15 [62.5%] patients) compared to the KY1005 groups (10 [37.0%] and 9 [33.3%] in the low and high dose groups, respectively). There were no other notable differences between treatment groups in baseline disease characteristics, including affected BSA, EASI, SCORAD, NRS for pruritus and prior exposure to dupilumab.

Table 8: Baseline Disease Characteristics (FAS)

Characteristic	Parameter	KY1005 Low Dose (N=27)	KY1005 High Dose (N=27)	Placebo (N=24)
Affected BSA (%)	Mean (SD)	55.6 (20.82)	47.6 (19.17)	52.5 (20.62)
	Median	51.5	40.5	55.3
EASI	Mean (SD)	32.9 (12.82)	28.4 (11.54)	32.8 (14.46)
	Median	29.8	24.1	28.9
EASI >21 at Baseline	n (%)	21 (77.8%)	20 (74.1%)	18 (75.0%)
SCORAD	Mean (SD)	69.0 (12.36)	66.2 (11.62)	67.6 (15.51)
	Median	68.7	63.8	64.2
vIGA score of 4	n (%)	10 (37.0%)	9 (33.3%)	15 (62.5%)
NRS for pruritus (itch)	Mean (SD)	6.9 (2.32)	6.7 (2.19)	7.4 (1.60)
	Median	7.5	7.0	8.0
Dupilumab prior exposure	n (%)	0	0	1 (4.2%)

SD=standard deviation

Primary Efficacy Endpoint

The primary efficacy endpoint was the percentage change in EASI from baseline to Day 113. An overall summary of the percentage change in EASI score from Baseline to Day 113 is provided in Table 9 (FAS and Per Protocol Set (PPS)), and percentage change in EASI score from Baseline over time is illustrated using least square mean (LSM) with 95% CI in **FIG. 4**. Reductions in EASI score from Baseline to Day 113 in the FAS were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups (LSM percentage change [95% CI] from Baseline, -80.12 [-95.55, -64.68] and -69.97 [-85.04, - 54.60] for the low and high dose groups, respectively) compared to placebo (-49.37 [-66.02, - 32.72]). This difference versus placebo was nominally statistically significant for the KY1005 low dose group (difference in LSM [95% CI], -30.75 [-53.43, -8.06]; p=0.009) but not for the high dose group (difference in LSM [95% CI], -20.60 [-43.08, 1.88]; p=0.072). Thus, an effect in the KY1005 treatment groups versus placebo was observed from Day 15 and was maintained until Day 113.

For the PPS, the change from Baseline to Day 113 in EASI score across all treatment groups was similar to that observed for the FAS (Table 9). As was observed for the FAS, greater reductions were observed in the KY1005 groups compared to placebo, and this difference versus placebo was nominally statistically significant for the KY1005 low dose group (difference in LSM [95% CI], -28.03 [-51.36, -4.70]; p=0.019) but not for the high dose group (difference in LSM [95% CI], -17.58 [-40.76, 5.60]; p=0.135).

The mixed model for repeated measures (MMRM) was performed on the PPS with the exclusion of one patient in the KY1005 high dose group to assess the impact of the exclusion of this patient in the PPS due to a protocol deviation. As observed for the FAS, greater reductions were observed in the KY1005 groups compared to placebo, and this difference versus placebo was nominally statistically significant for the KY1005 low dose group (difference in LSM [95% CI], -28.01

[-51.33, -4.69]; p=0.019) but not for the high dose group (difference in LSM [95% CI], - 17.01 [-40.20, 6.19]; p=0.148). No clinically relevant differences were observed when the sensitivity analysis was compared with the original PPS data.

Table 9: Percentage Change in EASI Score from Baseline to Day 113 MMRM (FAS and PPS)

	Parameter	FAS			PPS		
		KY1005 Low Dose (N=27)	KY1005 High Dose (N=27)	Placebo (N=24)	KY1005 Low Dose (N=27)	KY1005 High Dose (N=27)	Placebo (N=21)
Day 113	N	118	120	101	118	120	88
	LSM (95% CI)	-80.12 (-95.55, -64.68)	-69.97 (-85.04, -54.90)	-49.37 (-66.02, -32.72)	-80.41 (-95.73, -65.08)	-69.95 (-85.00, -54.90)	-52.37 (-69.96, -34.76)
	Differences in LSM, estimate (SE) [95% CI]	-30.75 (11.38) [-53.43, -8.06]	-20.60 (11.27) [-43.08, 1.88]		-28.03 (11.69) [-51.36, -4.70]	-17.58 (11.62) [-40.76, 5.60]	
	P-value	0.009	0.072		0.019	0.135	

CI=confidence interval; N=number of observations used; SE=standard error.

When Baseline EASI stratum (EASI≤21, EASI>21) was considered as a covariate, the change from Baseline to Day 113 in EASI score across all treatment groups was similar to that observed in the FAS for the primary analysis. Of note, three patients were randomized to the wrong EASI stratification due to their Baseline EASI values being changed after randomization. These patients were analyzed in the EASI subgroup analysis according to their planned stratification. As was observed for the primary analysis, greater reductions were observed in the KY1005 groups compared to placebo, and this difference versus placebo was nominally statistically significant for the KY1005 low dose group (difference in LSM [95% CI], -30.55 [-53.33, -7.77]; p=0.009) but not for the high dose group (difference in LSM [95% CI], -21.23 [-43.76, 1.31]; p=0.064). As documented in the Statistical Analysis Plan (SAP), the MMRM with country effect was not performed due to an insufficient number of patients per country.

The MMRM analysis of percentage change in EASI score was performed with the addition of rescue medication within the first month (yes/no) and rescue medication-by-treatment as fixed effects in the FAS to understand any impact of protocol permitted rescue use in the first 30 days. This analysis showed similar change from baseline to Day 113 in EASI score across all treatment groups to that observed for the primary analysis. As was observed for the primary analysis, greater reductions were observed in the KY1005 groups compared to placebo. This difference versus placebo was nominally statistically significant for both the KY1005 low dose group (difference in LSM [95% CI], -37.53 [-65.43, -9.63]; p=0.009) and high dose group (difference in LSM [95% CI], -28.43 [-56.35, -0.50]; p=0.046).

Secondary Efficacy Endpoints

The main secondary efficacy endpoint was the percentage and absolute change from baseline in EASI over time. A summary of the change in EASI score from baseline to Days 15, 29, 57, 85, 113 and the early termination visit in EASI score is summarized by treatment group in Table 10 for the FAS.

Progressive reductions in EASI score from Baseline to Days 15, 29, 57 and 85 (and Day 113) were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points.

Table 10: Change in EASI Score from Baseline to Days 15, 29, 57, 85, 113, and Early Termination Visit (FAS)

	Parameter	KY1005 Low Dose	KY1005 High Dose	Placebo
Baseline	n	27	27	24
EASI Score	Mean (SD)	32.87 (12.819)	28.44 (11.536)	32.77 (14.463)
	95% CI	27.80, 37.95	23.87, 33.00	26.66, 38.88
	Median	29.80	24.10	28.90
	Min, max	16.4, 63.6	16.1, 61.0	16.3, 65.7
Day 15	n	26	25	21
EASI score absolute change from Baseline	Mean (SD)	-10.67	-9.55 (11.655)	-3.27 (8.834)
	95% CI	-15.34, -6.00	-14.36, -4.74	-7.29, 0.75
	Median	-7.50	-8.90	-3.60
	Min, max	-37.6, 10.4	-42.2, 12.3	-22.2, 18.8
EASI score percentage change from Baseline	Mean (SD)	-30.58	-28.94 (33.753)	-15.16 (26.895)
	95% CI	-40.46, -20.71	-42.87, -15.00	-27.40, -2.91
	Median	-30.35	-34.20	-13.50
	Min, max	-84.7, 22.0	-92.5, 55.7	-60.1, 48.2
Day 29	n	25	26	22
EASI score absolute change from Baseline	Mean (SD)	-15.64	-11.32 (11.549)	-6.33 (8.356)
	95% CI	-21.37, -9.92	-15.98, -6.65	-10.03, -2.62
	Median	-13.20	-10.40	-6.90
	Min, max	-45.9, 8.1	-39.0, 13.9	-23.7, 10.2
	Parameter	**KY1005 Low Dose**	**KY1005 High Dose**	**Placebo**
EASI score percentage change from Baseline	Mean (SD)	-42.07 (28.495)	-37.29 (36.978)	-20.76 (28.318)
	95% CI	-53.83, -30.31	-52.22, -22.35	-33.32, -8.21
	Median	-43.20	-40.10	-22.85
	Min, max	-89.0, 33.8	-92.9, 72.0	-68.2, 41.5

Day 57	n	24	23	19
EASI score absolute change from Baseline	Mean (SD)	-19.13 (14.343)	-17.45 (13.330)	-12.18 (10.436)
	95% CI	-25.19, -13.08	-23.21, -11.68	-17.21, -7.15
	Median	-17.20	-11.90	-11.70
	Min, max	-51.7, 18.4	-57.8, -0.1	-39.4, 4.3
EASI score percentage change from Baseline	Mean (SD)	-58.07 (32.798)	-56.77 (26.880)	-38.43 (26.516)
	95% CI	-71.92, -44.22	-68.40, -45.15	-51.21, -25.65
	Median	-68.45	-52.70	-32.40
	Min, max	-98.6, 42.1	-96.6, -0.6	-82.4, 13.5
Day 85	n	22	23	18
EASI score absolute change from Baseline	Mean (SD)	-24.90 (12.588)	-21.43 (13.533)	-10.98 (9.768)
	95% CI	-30.49, -19.32	-27.28, -15.58	-15.84, -6.12
	Median	-24.10	-18.40	-10.30
	Min, max	-46.6, 3.5	-61.0, -5.3	-29.4, 4.3
EASI score percentage change from Baseline	Mean (SD)	-74.45 (23.790)	-71.06 (26.425)	-38.94 (30.860)
	95% CI	-85.00, -63.90	-82.49, -59.63	-54.29, -23.60
	Median	-76.85	-75.80	-36.45
	Min, max	-100.0, 8.0	-100.0, -21.5	-92.6, 13.5
Day 113	n	20	22	16
EASI score absolute change from Baseline	Mean (SD)	-25.97 (14.803)	-21.95 (14.132)	-15.50 (11.719)
	95% CI	-32.89, -19.04	-28.21, -15.68	-21.74, -9.26
	Median	-24.85	-21.30	-15.40
	Min, max	-48.9, 14.2	-61.0, 12.1	-32.0, 8.4
EASI score percentage change from Baseline	Mean (SD)	-79.66 (29.755)	-74.11 (32.875)	-55.21 (38.820)
	95% CI	-93.56, -65.73	-88.69, -59.54	-75.90, -34.53
	Median	-89.45	-79.20	-63.35
	Min, max	-100.0, 32.5	-100.0, 50.4	-100.0, 43.9
Early Termination Main Study	n	1	1	5
EASI score absolute change from Baseline	Mean (SD)	-12.90 (-)	19.90 (-)	-8.30 (9.443)
	95% CI	-	-	-20.02, 3.42
	Median	-12.90	19.90	-13.40
	Min, max	-12.9, -12.9	19.9, 19.9	-18.0, 3.1
EASI score percentage change from Baseline	Mean (SD)	-72.50 (-)	103.10 (-)	-24.58 (32.572)
	95% CI	-	-	-65.02, 15.86
	Median	-72.50	103.10	-22.10
	Min, max	-72.5, -72.5	103.1, 103.1	-71.0, 9.7

CI=confidence interval; Max=maximum; Min=Minimum; SD=standard deviation.

Percentage of Patients with at least 50%, 75% and 90% Reduction from Baseline in EASI (EASI 50, EASI 75 and EASI 90) at Days 15, 29, 57, 85 and 113

Bar charts illustrating EASI 50, EASI 75 and EASI 90 responders over time are presented in **FIG. 5A-C**. For this analysis, the values from early termination visits were assigned to the closest visit using the actual day on which the early termination visit was performed. If the closest visit was a visit that was performed, the value of the early termination was assigned to the next following visit.

Progressive increases in the percentages of patients with at least a 50%, 75% and 90% reduction from baseline in EASI were generally observed across all treatment groups, including placebo. However, the percentages were greater in the KY1005 groups compared to placebo at all time points (with the exception of EASI 90 at Days 15 and 29, where percentages were zero for both the KY1005 low dose and placebo groups).

For EASI 50, percentages were approximately 22% and 22% in the KY1005 low and high dose groups, respectively, versus 4% in the placebo group at Day 15; 33% and 37% (KY1005 groups) versus 13% (placebo) at Day 29; 59% and 52% (KY1005 groups) versus 25% (placebo) at Day 57; 74% and 63% (KY1005 groups) versus 25% (placebo) at Day 85; and 67% and 70% (KY1005 groups) versus 42% (placebo) at Day 113.

For EASI 75, percentages were approximately 4% and 7% in the KY1005 low and high dose groups, respectively, versus 0% in the placebo group at Day 15; 7% and 11% (KY1005 groups) versus 0% (placebo) at Day 29; 41% and 22% (KY1005 groups) versus 13% (placebo) at Day 57; 41% and 48% (KY1005 groups) versus 13% (placebo) at Day 85; and 59% and 52% (KY1005 groups) versus 25% (placebo) at Day 113.

For EASI 90, percentages were approximately 0% and 4% in the KY1005 low and high dose groups, respectively, versus 0% in the placebo group at Day 15; 0% and 7% (KY1005 groups) versus 0% (placebo) at Day 29; 7% and 19% (KY1005 groups) versus 0% (placebo) at Day 57; 22% and 30% (KY1005 groups) versus 4% (placebo) at Day 85; and 33% and 30% (KY1005 groups) versus 13% (placebo) at Day 113.

Percentage of Patients with a Response of 0 ('Clear') or 1 ('Almost Clear') at Day 113 and Over Time in vIGA Between Treatment Regimens

The percentage of patients with a response of 0 (clear) or 1 (almost clear) in vIGA at Days 15, 29, 57, 85 and 113, with corresponding analysis using a Cochran-Mantel-Haenszel test, is summarized for the FAS in Table 11. A bar chart of vIGA 0/1 responders over time is presented in **FIG. 6**. For this analysis, the values from early termination visits were assigned to the closest visit using the actual day on which the early termination visit was performed. If the closest visit was a

visit that was performed, the value of the early termination was assigned to the next following visit.

Progressive increases in the percentages of vIGA 0/1 responders over time were generally observed in the KY1005 treatment groups, but not in the placebo group. By Day 113, the percentage of vIGA 0/1 responders was 44.4% (12/27) and 37.0% (10/27) in the KY1005 low and high dose groups, respectively, compared with 8.3% (2/24) in the placebo group. Thus, treatment with KY1005 was associated with nominally statistically significant increased numbers of vIGA 0/1 responders compared to placebo (Cochran-Mantel-Haenszel p<0.001 for both the low and high dose groups).

FIG. 7 represents all patients who achieved a vIGA0/1 at Week 16 and were assessed for efficacy during the safety follow up period. The scores within the table are the EASI scores at each visit. This figure shows that in those subjects who achieved vIGA0/1 at day 113, there was evidence of long and sustained response up to 5.5 months following last dose (~70% of those receiving KY1005).

Table 11: Percentage of Patients with a Response of 0 (Clear) or 1 (Almost Clear) in vIGA at Days 15, 29, 57, 85 and 113 (FAS)

Parameter	Time Point	KY1005 Low Dose (N=27)		KY1005 High Dose (N=27)		Placebo (N=24)	
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
vIGA of 0 (Clear) or 1 (Almost clear)	Day 15	0 (0.0%)	0.00, 0.00	0 (0.0%)	0.00, 0.00	0 (0.0%)	0.00, 0.00
	Day 29	0 (0.0%)	0.00, 0.00	3 (11.1%)	0.00, 22.97	0 (0.0%)	0.00, 0.00
	Day 57	4 (14.8%)	1.42, 28.21	3 (11.1%)	0.00, 22.97	0 (0.0%)	0.00, 0.00
	Day 85	8 (29.6%)	12.41, 46.85	9 (33.3%)	15.55, 51.11	0 (0.0%)	0.00, 0.00
	Day 113	12 (44.4%)	25.70, 63.19	10 (37.0%)	18.82, 55.25	2 (8.3%)	0.00,19.39
Cochran-Mantel-Haenszel test versus placebo		<0.001		<0.001			

CI=confidence interval

Change in vIGA from Baseline to Day 113 and over time

All patients had a vIGA of 3 (moderate) or 4 (severe) at Baseline, in line with the study inclusion criteria. Of note, the number of patients with a vIGA score of 4 (severe) at baseline was higher in the placebo group (15 [62.5%] patients) compared to the KY1005 groups (10 [37.0%] and 9 [33.3%] in the low and high dose groups, respectively).

Progressive improvements in vIGA from Baseline to Days 15, 29, 57, 85 and 113 were observed across all treatment groups, including placebo. However, the improvements were generally more pronounced in the KY1005 groups compared to placebo. For example, at Day 15, shifts in vIGA from 4 (severe) to 3 (moderate) were reported for 70.0% and 66.7% of the patients in the KY1005

low and high dose groups, respectively, compared with 25.0% of the patients in the placebo group. At Day 113, shifts in vIGA from 4 (severe) to 3 (moderate), 2 (mild), 1 (almost clear) and 0 (clear), respectively, were reported for 12.5%, 12.5%, 50.0% and 12.5% of the patients in the KY1005 low dose group and 12.5%, 12.5%, 37.5% and 12.5% of the patients in the KY1005 high dose group, compared with 37.5%, 37.5%, 0% and 0% of the patients in the placebo group. Greater improvements in vIGA in the KY1005 groups compared to placebo were similarly seen for patients with a vIGA of 3 (moderate) at baseline.

Change in SCORAD Index from Baseline to Day 113 and Over Time

Analysis of the percentage change from baseline in SCORAD Index between treatment regimens (MMRM analysis) is presented in Table 12 and **FIG. 8**. Progressive reductions in SCORAD Index from Baseline to Days 29, 57, 85 and 113 were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points: LSM percentage change (95% CI) in SCORAD Index at Day 113 was -60.30 (-72.57, -48.04) and -58.96 (-71.04, -46.87) for the KY1005 low and high dose groups, respectively, compared to placebo (-36.79 [-49.94, -23.65]). These differences versus placebo were nominally statistically significant for both the KY1005 low dose group (difference in LSM [95% CI], -23.51 [-41.50, -5.52]; p=0.011) and the KY1005 high dose group (difference in LSM [95% CI], - 22.16 [-40.00, -4.32]; p=0.016). Thus, an effect in the KY1005 treatment groups versus placebo was observed from Day 29 and maintained until Day 113.

Table 12: Percentage Change from Baseline in SCORAD Index Between Treatment Regimes MMRM (FAS)

Time Point	Parameter	KY1005 Low Dose (N=27)	KY1005 High Dose (N=27)	Placebo (N=24)
Day 29	LSM (95% CI)	-25.14 (-33.84, -16.43)	-27.65 (-36.18, -19.13)	-12.16 (-21.23, -3.10)
	Differences in LSM, estimate (SE) [95% CI]	-12.97 (6.30) [-25.54, -0.40]	-15.49 (6.24) [-27.93, -3.05]	
	P-value	0.043	0.015	
Day 57	LSM (95% CI)	-43.51 (-53.31, -33.72)	-37.05 (-47.07, -27.03)	-24.22 (-34.59, -13.84)
	Differences in LSM, estimate (SE) [95% CI]	-19.30 (7.16) [-33.57, -5.02]	-12.83 (7.23) [-27.26, 1.59]	
	P-value	0.009	0.080	
Day 85	LSM (95% CI)	-55.48 (-66.94, -44.03)	-52.02 (-63.28, -40.75)	-26.95 (-39.24, -14.65)
	Differences in LSM, estimate (SE) [95% CI]	-28.54 (8.43) [-45.35, -11.73]	-25.07 (8.36) [-41.74, -8.40]	
	P-value	0.001	0.004	

Day 113	LSM (95% CI)	-60.30 (-72.57, -48.04)	-58.96 (-71.04, -46.87)	-36.79 (-49.94, -23.65)
	Differences in LSM, estimate (SE) [95% CI]	-23.51 (9.02) [-41.50, -5.52]	-22.16 (8.95) [-40.00, -4.32]	
	P-value	0.011	0.016	

CI=confidence interval; SE=standard error.

Change in Affected BSA from Baseline to Day 113 and Over Time

Percentage change in affected BSA from Baseline over time is illustrated using LSM with 95% CI in **FIG. 9**. Progressive reductions in affected BSA from Baseline to Days 29, 57, 85 and 113 were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points: least square means percentage change (95% CI) in affected BSA at Day 113 was -78.07 (-92.35, -63.79) and -71.97 (-86.10, -57.84) for the KY1005 low and high dose groups, respectively, compared to placebo (-41.58 [-57.35, -25.80]). These differences versus placebo were nominally statistically significant for both the KY1005 low dose group (difference in LSM [95% CI], -36.49 [-57.84, -15.14]; p=0.001) and the KY1005 high dose group (difference in LSM [95% CI], -30.39 [-51.50, -9.29]; p=0.005) in the FAS. Thus, an effect in the KY1005 treatment groups versus placebo was observed from Day 29 and maintained until Day 113.

Change in PO-SCORAD Index from Baseline to Day 113 and Over Time

Percentage change in PO-SCORAD Index from Baseline over time is illustrated using LSM with 95% CI in **FIG. 10**. Progressive reductions in PO-SCORAD Index from Baseline to Days 15, 29, 57, 64, 85 and 113 were generally observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at nearly all time points: by Day 113, LSM percentage change (95% CI) in PO-SCORAD Index was -55.16 (-69.11, -41.21) and -43.04 (-56.41, -29.67) in the KY1005 low and high dose groups, respectively, versus -23.96 (-38.36, -9.46) in the placebo group. These differences versus placebo were nominally statistically significant for the KY1005 low dose group (difference in LSM [95% CI], -31.20 [-51.29, -11.10]; p=0.003) and not for the KY1005 high dose group (difference in LSM [95% CI], -19.07 [-38.86, 0.71]; p=0.059).

Change in DLQI from Baseline to Day 113 and Over Time

Percentage change in DLQI total score from baseline over time is illustrated using LSM with 95% CI in **FIG. 11**. Progressive reductions in DLQI total score from baseline to Days 15, 29, 57, 64, 85 and 113 were generally observed across all treatment groups, including placebo. There were generally no clear differences between the treatment groups in the magnitude of the reductions, although there was a trend for greater reductions in the KY1005 treatment groups compared to

placebo at Days 85 and 113: by Day 113, LSM percentage change (95% CI) in DLQI total score was -52.99 (-75.31, -30.67) and -59.15 (-80.32, -37.99) in the KY1005 low and high dose groups, respectively, versus -20.51 (-44.95, 3.93) in the placebo group. These differences versus placebo were not significant for the KY1005 low dose group (difference in LSM [95% CI], -32.48 [-65.82, 0.86]; p=0.056) and nominally statistically significant for the KY1005 high dose group (difference in LSM [95% CI], -38.65 [-71.05, -6.24]; p=0.020).

Improvements in DLQI total score, by category, were generally observed post-baseline across the treatment groups, including placebo. However, greater improvements were generally observed in the KY1005 groups compared to placebo. For example, by Day 113, the percentage of patients in the category "no effect at all on patient's life" was approximately 33% (6/18) and 38% (8/21) for the KY1005 low and high dose groups, respectively, compared with 6% (1/16) for the placebo group; conversely, the percentage of patients in the category "extremely large effect" was 0% for both KY1005 groups compared with 19% (3/16) for the placebo group.

Change in NRS for Pruritus from Baseline to Day 113 and Over Time

Analyses of the change in NRS for pruritus from Baseline to Day 113 and over time were performed using the mean values of absolute NRS values calculated per week, i.e., for the corresponding day and the previous 6 days, if at least four values were available. Using the average per week approach, post-hoc analyses of the percentage of patients with a best improvement in NRS for pruritus of at least 3 and 4 units with a baseline NRS for pruritus of at least 3 and at least 4, respectively, were performed. For all analyses, the baseline value was considered as the value taken on the date of the baseline visit.

Percentage change in mean weekly NRS for pruritus from Baseline over time is illustrated using LSM with 95% CI in **FIG. 12**. Progressive reductions in weekly mean values for NRS for pruritus from Baseline to Days 15, 29, 57, 85 and 113 were generally observed across all treatment groups, including placebo. There were no clear differences between the treatment groups in the magnitude of the reductions at any time point, and none of the comparisons of percentage change in NRS for pruritus between KY1005 groups and placebo revealed a nominally statistically significant difference.

In a post-hoc analysis for patients with a Baseline NRS of at least 3, the percentage of patients with a best improvement in NRS for pruritus by average per week of at least 3 units at week of Day 113 and overall is summarized in Table 13.

Table 13: Percentage of Patients with a Best Improvement in NRS for Pruritus of at Least 3 Units Based on Patients with a Baseline NRS of at Least 3 (FAS)

	KY1005 Low Dose (N=20)	KY1005 High Dose (N=25)	Placebo (N=21)

	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients with a best improvement in NRS of at least 3						
Week of Day 113	11 (55.0%)	33.20, 76.80	13 (52.0%)	32.42, 71.58	7 (33.3%)	13.17, 53.50
Overall	13 (65.0%)	44.10, 85.90	18 (72.0%)	54.40, 89.60	14 (66.7%)	46.50, 86.83

CI=confidence interval

Overall, the percentage of patients with a best improvement in NRS for pruritus by average per week of at least 3 units was greater in the KY1005 high dose group (72.0% [18/25; 95% CI, 54.40, 89.60]) compared to the KY1005 low dose group (65.0% [13/20; 95% CI, 44.10, 85.90]) and the placebo group (66.7% [14/21; 95% CI, 46.50, 86.83]). Similar results to the week of Day 113 data were observed for the EASI>21 stratum, but the low numbers of patients included in the EASI ≤21 stratum makes it difficult to draw meaningful conclusions from this subgroup.

In another post-hoc analysis for patients with a baseline NRS of at least 4, the percentage of patients with a best improvement in NRS for pruritus by average per week of at least 4 units by week and overall is summarized in Table 14. Progressive improvements in NRS for pruritus were observed across all treatment groups, including placebo. However, greater improvements were observed in the KY1005 groups compared to placebo.

Table 14: Percentage of Patients with a Best Improvement in NRS for Pruritus by Average per Week of at Least 4 Units by Week and Overall Based on Patients with a Baseline NRS of at Least 4 (FAS)

	KY1005 Low Dose (N=19)		KY1005 High Dose (N=24)		Placebo (N=21)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients with a best improvement in NRS of at least 4						
Week of Day 113	9 (47.4%)	24.92, 69.82	9 (37.5%)	18.13, 56.87	4(19.0%)	2.25, 35.84
Overall	11 (57.9%)	35.69, 80.10	15 (62.5%0	43.13, 81.87	8(38.1%)	17.33, 58.87

CI=confidence interval

Overall, results were observed were 57.9% (11/19; 95% CI, 35.69, 80.10) and 62.5% (15/24; 95% CI, 43.13, 81.87) for the KY1005 low and high dose groups, respectively, compared to placebo (38.1% [8/21; 95% CI, 17.33, 58.87]). Similar results were observed for the EASI >21 and EASI ≤21 strata to those observed in the FAS, but the low numbers of patients included in the EASI ≤21 stratum makes it difficult to draw meaningful conclusions from this subgroup.

The overall conclusions from the post-hoc NRS analyses for pruritus were similar to those from the pre-specified analysis, with no clear differences between the treatment groups when considering the FAS population as a whole. However, in patients with severe disease at baseline (EASI >21), a difference of approximately 20 percentage points was observed between both KY1005

high and low dose groups (58.8% each) compared to placebo (35.7%) when considering the high hurdle response of at least 4 units in patients with a Baseline NRS of at least 4 (Table 15).

Table 15: Percentage of Patients with a Best Improvement in NRS for Pruritus by Average per Week of at Least 4 Units by Week and Overall Based on Patients with a Baseline NRS of at Least 4 (EASI >21)

	KY1005 Low Dose (N=17)		KY1005 High Dose (N=17)		Placebo (N=14)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Patients with a best improvement in NRS of at least 4						
Week of Day 113	8 (47.1%)	23.33, 70.79	5(29.4)	7.75, 51.07	2(14.3%)	0.00, 32.62
Overall	10 (58.8%)	35.43, 82.22	10(58.8%)	35.43, 82.22	5(35.7%)	10.61, 60.81

CI=confidence interval

Exploratory Efficacy Analysis

Exploratory efficacy analyses were completed in the subset of patients in the FAS who were defined as responders at Day 113 (i.e., vIGA of 0 or 1), which comprised 12, 10 and 2 patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively (See section "Change in vIGA from Baseline to Day 113 and over time" above). Of note, if the vIGA score at Day 113 was missing, the next available vIGA score was used to determine whether the patient was a responder (vIGA 0/1).

Percentage and Absolute EASI Change from Day 113 Over Time (i.e., Day 169 and Day 253)

A summary of change in EASI score from Baseline to Days 113, 169 and 253 for patients who were defined as responders (vIGA 0/1) at Day 113 is provided in Table 15a.

Table 15a: Change in EASI Score from Baseline to Days 113, 169 and 253 (Responders)

	Parameter	KY1005 Low Dose (N=12)	KY1005 High Dose (N=10)	Placebo (N=2)
Day 113	n	12	10	2
EASI score absolute change from Baseline	Mean (SD)	-32.21 (8.686)	-30.18 (13.748)	-27.90 (5.798)
	95% CI	-37.73, -26.69	-40.02, -20.34	-80.00, 24.20
	Median	-30.50	-24.40	-27.90
	Min, max	-45.9, -18.9	-61.0, -16.5	-32.0, -23.8
EASI score percentage change from Baseline	Mean (SD)	-93.47 (4.242)	-94.66 (6.662)	-96.50 (4.950)
	95% CI	-96.16, -90.77	-99.43, -89.89	-140.97, -52.03
	Median	-93.40	-97.00	-96.50
	Min, max	-100.0, -86.8	-100.0, -78.8	-100.0, -93.0
Day 169	n	12	10	2
EASI score absolute change from Baseline	Mean (SD)	-32.28 (8.121)	-30.57 (14.093)	-24.25 (2.333)
	95% CI	-37.44, -27.12	-40.65, -20.49	-45.22, -3.28
	Median	-32.25	-24.70	-24.25
	Min, max	-47.2, -19.5	-60.8, -17.1	-25.9, -22.6
EASI score percentage change from Baseline	Mean (SD)	-94.34 (7.035)	-95.71 (8.489)	-85.15 (13.930)
	95% CI	-98.81, -89.87	-101.78, -89.64	-210.31, 40.01
	Median	-97.30	-98.95	-85.15
	Min, max	-100.0, -75.0	-100.0; -73.1	-95.0; -75.3
Day 253	n	11	8	2
EASI score absolute change from Baseline	Mean (SD)	-28.17 (9.135)	-24.65 (6.813)	-25.70 (8.061)
	95% CI	-34.31, -22.04	-30.35, -18.95	-98.13, 46.73
	Median	-27.20	-22.75	-25.70
	Min, max	-45.6, -12.5	-36.8, -17.1	-31.4, -20.0
EASI score percentage change from Baseline	Mean (SD)	-83.85 (20.220)	-94.10 (9.178)	-87.65 (5.162)
	95% CI	-97.44, -70.27	-101.77, -86.43	-134.03, -41.27
	Median	-94.70	-96.65	-87.65
	Min, max	-100.0, -38.7	-100.0, -72.2	-91.3, -84.0

AD=atopic dermatitis; CI=confidence interval; EASI=Eczema Area and Severity Index; max=maximum; min=minimum; SD=standard deviation.

Note: The total EASI score is the weighted total of the section EASI using the weights 10% (head), 20% (upper extremities), 30% (trunk) and 40% (lower extremities). The minimum possible EASI score is zero and the maximum possible EASI score is 72, where a higher score indicates increased extent and severity of AD.

For responders, reductions in EASI score from Baseline to Days 113, 169 and 253 were observed in all treatment groups, including placebo.

Mean percentage change (95% CI) in EASI score at Day 169 was -94.34 (-98.81, -89.87), -95.71 (-101.78, -89.64) and -85.15 (-210.31, -40.01) for the KY1005 low dose (n=12), KY1005 high dose (n=10) and placebo (n=2) groups, respectively, and at Day 253 was -83.85 (-97.44, -70.27), -94.10 (-101.77, -86.43) and -87.65 (-134.03, -41.27) for the KY1005 low dose (n=11), KY1005 high dose (n=8) and placebo (n=2) groups, respectively.

EASI 50, 75 and 90 from Day 113 Over Time

The percentages of patients with at least a 50%, 75% and 90% reduction from Baseline in EASI at Days 113, 169 and 253 are summarised by treatment group for patients who were defined as responders (vIGA 0/1) at Day 113 in an overall summary provided in Table 15b.

All responders in all treatment groups had an EASI 50 response at Days 113 and 169. At Day 253, percentages were approximately 83%, 80% and 100% in the KY1005 low dose, KY1005 high dose and placebo groups, respectively.

All responders in all treatment groups had an EASI 75 response at Days 113 and 169, with the exception of the KY1005 high dose group at Day 169 (9/10). At Day 253, percentages were approximately 67% (8/12), 70% (7/10) and 100% (2/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively.

For EASI 90, percentages were approximately 75% (9/12), 80% (8/10) and 100% (2/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively, at Day 113; 92% (11/12), 90% (9/10) and 50% (1/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively, at Day 169; and 50% (6/12), 70% (7/10) and 50% (1/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively, at Day 253.

Table 15b: Percentage of Patients with a 50%, 75% and 90% Reduction from Baseline at Days 113, 169 and 253 in EASI Score (Responders)

Parameter	Time Point	KY1005 Low Dose (N=12)		KY1005 High Dose (N=10)		Placebo (N=2)	
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
50% reduction from Baseline in EASI score	Day 113	12(100.0%)	100.00,100.00	10 (100.0%)	100.00,100.00	2 (100.0%)	100.00, 100.00
	Day 169	12(100.0%)	100.00,100.00	10 (100.0%)	100.00,100.00	2 (100.0%)	100.00, 100.00
	Day 253	10(83.3%)	62.25,100.00	8 (80.0%)	55.21,100.00	2 (100.0%)	100.00, 100.00

Parameter	Time Point	KY1005 Low Dose (N=12)		KY1005 High Dose (N=10)		Placebo (N=2)	
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
75% reduction from Baseline in EASI score	Day 113	12(100.0%)	100.00,100.00	10 (100.0%)	100.00,100.00	2 (100.0%)	100.00, 100.00
	Day 169	12(100.0%)	100.00,100.00	9 (90.0%)	71.41,100.00	2 (100.0%)	100.00, 100.00
	Day 253	8 (66.7%)	39.99,93.34	7 (70.0%)	41.60,98.40	2 (100.0%)	100.00, 100.00
90% reduction from Baseline in EASI score	Day 113	9 (75.0%)	50.50,99.50	8 (80.0%)	55.21,100.00	2 (100.0%)	100.00, 100.00
	Day 169	11(91.7%)	76.03,100.00	9 (90.0%)	71.41,100.00	1 (50.0%)	0.00, 100.00
	Day 253	6 (50.0%)	21.71,78.29	7 (70.0%)	41.60,98.40	1 (50.0%)	0.00, 100.00

CI=confidence interval; EASI=Eczema Area and Severity Index. Note: When lower CI is negative, it has been bound to 0.0. Note: When upper CI is greater than 100, it has been bound to 100.0.

vIGA from Day 113 Over Time

For patients who were defined as responders (vIGA 0/1) at Day 113, the percentages of patients in each vIGA category at Days 113, 169 and 253 are summarised in Table 15c.

At Day 169, one (8.3%) patient each in the KY1005 low dose group had a vIGA of 2 (mild) and 3 (moderate); one (10.0%) patient in the KY1005 high dose group had a vIGA of 2 (mild); and one (50.0%) patient in the placebo group had a vIGA of 2 (mild); the remaining patients (10, 9 and 1, respectively) still had a vIGA of 0 (clear) or 1 (almost clear).

At Day 253, three (27.3%) patients in the KY1005 low dose group had a vIGA of 3 (moderate); one (12.5%) patient in the KY1005 high dose group had a vIGA of 2 (mild); and one (50.0%) patient in the placebo group had a vIGA of 2 (mild); the remaining patients (8, 7 and 1, respectively) still had a vIGA of 0 (clear) or 1 (almost clear).

Table 15c: Percentage of Patients in vIGA Categories Between Treatment Regimens at Days 113, 169 and 253 (Responders)

	KY1005 Low Dose (N=12)	KY1005 High Dose (N=10)	Placebo (N=2)

Time Point		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Day 113	n	12		10		2	
	0 - Clear	2 (16.7%)	0.00,37.75	3 (30.0%)	1.60,58.40	1 (50.0%)	0.00, 100.00
	1 - Almost clear	10(83.3%)	62.25,100.00	7 (70.0%)	41.60,98.40	1 (50.0%)	0.00, 100.00
	2 - Mild	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
	3 - Moderate	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
	4 - Severe	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
Day 169	n	12		10		2	
	0 - Clear	3 (25.0%)	0.50,49.50	4 (40.0%)	9.64,70.36	0 (0.0%)	0.00, 0.00
	1 - Almost clear	7 (58.3%)	30.44,86.23	5 (50.0%)	19.01,80.99	1 (50.0%)	0.00, 100.00
	2 - Mild	1 (8.3%)	0.00,23.97	1 (10.0%)	0.00,28.59	1 (50.0%)	0.00, 100.00
	3 - Moderate	1 (8.3%)	0.00,23.97	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
	4 - Severe	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
Day 253	n	11		8		2	
	0 - Clear	2 (18.2%)	0.00,40.97	2 (25.0%)	0.00,55.01	0 (0.0%)	0.00, 0.00
	1 - Almost clear	6 (54.5%)	25.12,83.97	5 (62.5%)	28.95,96.05	1 (50.0%)	0.00, 100.00
	2 - Mild	0 (0.0%)	0.00,0.00	1 (12.5%)	0.00,35.42	1 (50.0%)	0.00, 100.00

	3 - Moderate	3 (27.3%)	0.95,53.59	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00
	4 - Severe	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00,0.00	0 (0.0%)	0.00, 0.00

CI=confidence interval; vIGA=validated Investigator Global Assessment.
Note: When lower CI is negative, it has been bound to 0.0. Note: When upper CI is greater than 100, it has been bound to 100.0.

Percentage of Patients with a Response of vIGA of 0 or 1 from Day 113 Over Time

The percentage of patients with a response of 0 (clear) or 1 (almost clear) in vIGA at Days 113, 169 and 253 is summarised for patients who were defined as responders (vIGA 0/1) at Day 113 in Table 15d.

Table 15d: Percentage of Patients with a Response of 0 (Clear) or 1 (Almost Clear) in vIGA at Days 113, 169 and 253 (Responders)

Parameter	Time Point	KY1005 Low Dose (N=12)		KY1005 High Dose (N=10)		Placebo (N=2)	
		n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
vIGA of 0 (Clear) or 1 (Almost clear)	Day 113	12 (100.0%)	100.00, 100.00	10 (100.0%)	100.00, 100.00	2 (100.0%)	100.00, 100.00
	Day 169	10 (83.3%)	62.25, 100.00	9 (90.0%)	71.41, 100.00	1 (50.0%)	0.00, 100.00
	Day 253	8 (66.7%)	39.99, 93.34	7 (70.0%)	41.60, 98.40	1 (50.0%)	0.00, 100.00

CI=confidence interval; vIGA=validated Investigator Global Assessment.

Note: Numbers on columns represent number of patients with a positive response (vIGA of '0' or '1' at Day 'xxx' = Yes). Note: When lower CI is negative, it has been bound to 0.0. Note: When upper CI is greater than 100, it has been bound to 100.0.

At Day 169, the percentage of vIGA 0/1 responders was 83.3% (10/12), 90.0% (9/10) and 50.0% (1/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively. At Day 253, the percentage of vIGA 0/1 responders was 66.7% (8/12), 70.0% (7/10) and 50.0% (1/2) in the KY1005 low dose, KY1005 high dose and placebo groups, respectively.

Drug Serum Concentration Analysis

Serum KY1005 concentration versus time data are presented using the geometric mean in **FIG. 13** and **FIG. 14** (study extension).

For the main study, serum concentration profiles for KY1005 were similar between the KY1005 groups, with higher concentrations recorded for the KY1005 high dose group compared to the low dose group. With repeated I.V. administration, serum concentrations peaked rapidly and subsequently decreased after each dose.

As observed in the main study, serum concentration profiles for patients who entered the study extension were similar between the KY1005 groups, with higher KY1005 concentrations recorded for the KY1005 high dose group compared to the low dose group. Following the fourth infusion on Day 85, serum concentrations steadily decreased up to Day 253.

Serum Pharmacokinetic Analysis

Main Study (to Day 113):

Derived serum PK parameters for KY1005 in the main study are summarized in Table 16. Serum concentrations of KY1005 increased rapidly following dosing (see **FIG. 13**), with a median t_{max} of 0.03 days for both the KY1005 low and high doses, after both the first and fourth (third maintenance) infusions, and an approximately dose proportional relationship for C_{max}, AUC_{0-28} and AUC_{0-inf} was observed. Following each dose, serum concentrations steadily decreased in a biphasic manner, with geometric mean $t_{1/2}$ values after the first infusion that were similar for the low (21.25 days) and high (24.46 days) doses. The AUC_{extrap}(%) was large (geometric mean, 35.84% and 39.23% for the low and high dose, respectively), which suggests that the reported AUC_{0-inf} and $t_{1/2}$ may not be reliable.

Table 16: Serum PK Parameters of KY1005 (PK Population) (Main Study)

Parameter			KY1005 Low Dose (N=29)	KY1005 High Dose (N=30)
C_{max} (ng/mL)	After first infusion	n	29	30
		Geometric mean (95% CI)	62,456.97 (54,385.916, 71,725.801)	153,299.41 (143,441.855, 163,834.383)
		Min, max	15,231.5, 106,325.7	104,366.1, 209,120.7
	After fourth infusion	n	21	22
		Geometric mean (95% CI)	46,251.21 (38,892.865, 55,001.726)	126,248.15 (111,684.117, 142,711.398)
		Min, max	22,259.2, 90,752.0	81,638.8, 304,976.5
	After first infusion	n	29	30
		Median	0.03	0.03
		Min, max	0.0, 0.2	0.0, 0.2
		n	21	22

t_{max} (day)	After fourth infusion	Median	0.03	0.03
		Min, max	0.0; 0.2	0.0 ; 0.2
$t_{1/2}$	After first infusion (day)	n	25	27
		Geometric mean (95% CI)	21.25 (18.931, 23.858)	24.46 (22.014, 27.170)
		Min, max	10.7, 34.9	10.8, 35.4
C_{min} (ng/mL)	After first infusion	n	26	27
		Geometric mean (95% CI)	13,470.53 (10,906.620, 16,637.156)	41,394.53 (36,123.340, 47,434.904)
		Min, max	3,396.6, 36,213.5	21,620.3, 109,140.0
	After second infusion	n	24	23
		Geometric mean (95% CI)	14,061.17 (11,408.279, 17,330.970)	42,465.62 (37,407.532, 48,207.635)
		Min, max	3,176.2, 30,221.4	22,100.0, 70,221.4
	After third infusion	n	22	22
		Geometric mean (95% CI)	12,320.94 (8,881.177, 17,092.959)	44,016.54 (39,125.273, 49,519.290)
		Min, max	1,261.9, 29,377.1	23,811.2, 71,979.2
	After fourth infusion	n	20	21
		Geometric mean (95% CI)	12,653.30 (9,054.512, 17,682.467)	43,078.75 (38,269.947, 48,491.809)
		Min, max	1,301.2, 29,857.7	26,047.3, 65,983.9
C_{45} (ng/mL)	After first infusion	n	29	30
		Geometric mean (95% CI)	59,624.35 (52,239.076, 68,053.707)	149,304.53 (139,527.726, 159,766.410)
		Min, max	15,231.5, 93,711.4	99,425.1, 209,120.7
	After second infusion	n	26	27
		Geometric mean (95% CI)	44,449.66 (38,630.121, 51,145.900)	103,004.25 (88,670.241, 119,655.422)
		Min, max	14,655.4, 71,812.5	26,957.0, 149,235.7
	After third infusion	n	24	23
		Geometric mean (95% CI)	42,253.84 (34,556.654, 51,665.517)	118,017.27 (107,339.641, 129,757.062)
		Min, max	12,282.9, 103,391.1	75,930.9, 166,144.2
	After fourth infusion	n	21	22
		Geometric mean (95% CI)	39,327.14 (27,077.623, 57,118.173)	122,207.32 (107,528.541, 138,889.897)
		Min, max	1,484.6, 90,752.0	77,203.9, 304,976.5
AUC_{0-28} (ng/mL*day)	After first infusion	n	26	28
		Geometric mean (95% CI)	686,940.88 (590,166.320, 799,584.390)	1,883,507.76 (1,727,579.712, 2,053,509.580)
		Min, max	182,592.7, 1,250,598.2	1,239,102.4, 2,804,778.9

	After fourth infusion	n	20	21
		Geometric mean (95% CI)	644,224.34 (528,261.893, 785,642.513)	1,898,152.07 (1,724,488.487, 2,089,304.346)
		Min, max	268,463.7, 1,094,156.8	1,307,220.3, 2,603,856.9
AUC_{0-inf} (ng/mL*day)	After first infusion	n	25	27
		Geometric mean (95% CI)	1,117,227.16 (943,484.260, 1,322,964.871)	3,313,855.91 (2,917,920.239, 3,763,516.513)
		Min, max	308,344.7, 1,725,098.3	1,600,199.5, 5,682,149.8
AUC_{extrap}(%)	After first infusion	n	25	27
		Geometric mean (95% CI)	35.84 (31.273, 41.084)	39.23 (32.565, 47.264)
		Min, max	12.4, 52.2	4.6, 56.2
λz	After first infusion (1/day)	n	25	27
		Geometric mean (95% CI)	0.03 (0.029, 0.037)	0.03 (0.024, 0.031)
		Min, max	0.0, 0.1	0.0, 0.1

λz=terminal rate constant; AUC_{0-28}=area under the serum concentration-time curve in dosing interval; AUC_{0-inf}=area under the serum concentration-time curve extrapolated to infinity; $AUC_{extrap(\%)}$=area under the serum concentration-time curve percentage extrapolated area; CI=confidence interval; C_{max}=maximum observed serum concentration; C_{min}=trough concentration; max=maximum; min=minimum; PK=pharmacokinetic(s); $t_{1/2}$=apparent terminal half-life; SD=standard deviation; t_{max}=time to maximum observed serum concentration.

Geometric mean C_{max} after the first infusion of KY1005 was 62,456.97 and 153,299.41 ng/mL for the low and high doses, respectively, and after the fourth (third maintenance) infusion was 46,251.21 and 126,248.15 ng/mL, respectively. Peak concentrations (45 minutes after the start of all infusions, using scheduled time points) following each maintenance dose (Days 29, 57 and 85) were slightly lower than those obtained following the loading dose. Minimum geometric mean serum concentrations remained above 10,000 ng/mL in both dose cohorts.

C_{max} was greater following the KY1005 high dose compared to the low dose. However, AUC_{0-28} and C_{min} (trough) levels were similar when first (loading) and fourth (third maintenance) dose exposures were compared. Minimal accumulation was observed across the total four doses administered every 28 days.

In general, the mean serum concentration profile for KY1005 was dose proportional, where the 2.5-fold increase in dose attained an approximately 2.5-fold increase in exposure as measured by C_{max} and AUC_{0-28}. No target mediated drug disposition was apparent in the two dose cohorts across the total four doses administered.

Study Extension (from Day 113):

Derived serum PK parameters for KY1005 in the study extension are summarized in Table 17. Following the fourth infusion, serum concentrations of KY1005 steadily decreased, and an

approximately dose proportional relationship for $AUC_{0\text{-}inf}$ was observed. Geometric mean $t_{1/2}$ values were similar for the low (23.04 days) and high (28.02 days) doses. The $t_{1/2}$ values are more accurate than those derived from the main study after the first infusion, calculated using $AUC_{0\text{-}inf}$ values based on data up to 28 days after dosing only, since AUC_{extrap}(%) was <5%. Similar accumulation index, calculated after the fourth dose (about 2-fold), and Vd (about 5 L) was observed for the two KY1005 dose groups. Geometric mean concentrations (95% CI) on Day 253 (C_{min}) were 365.63 ng/mL (163.823, 816.020) in the KY1005 low dose group and 1,739.90 ng/mL (884.622; 3,422.103) in the KY1005 high dose group (**FIG. 14**). No target mediated drug disposition was apparent from the PK profiles up to 168 days after the last dose for either of the two KY1005 dose groups.

Table 17: Serum PK Parameters of KY1005 (PK Population) (Study Extension)

Parameter		KY1005 Low Dose	KY1005 High Dose
AI (expected) after fourth infusion	n	15	12
	Geometric mean (95% CI)	1.78 (1.619, 1.946)	2.01 (1.834, 2.211)
	Min, max	1.3, 2.3	1.5, 2.5
$AUC_{0\text{-}inf}$ (ng/mL*day) after fourth infusion	n	15	12
	Geometric mean (95% CI)	1,272,912.22 (975,475.562, 1,661,041.621)	3,884,561.93 (3,236,022.502, 4,663,076.769)
	Min, max	371,333.5, 2,334,167.2	2,405,791.7, 5,989,019.3
AUC_{extrap}(%) after fourth infusion	n	15	12
	Geometric mean (95% CI)	2.00 (0.751, 5.327)	4.14 (1.711, 10.007)
	Min, max	0.1, 40.5	0.7, 47.5
C_L (mL/day) after fourth infusion	n	20	21
	Geometric mean (95% CI)	155.22 (127.283, 189.299)	131.71 (119.658, 144.972)
	Min, max	91.4, 372.5	96.0, 191.3
C_{avg} (ng/mL) after fourth infusion	n	20	21
	Geometric mean (95% CI)	23,008.01 (18,866.497, 28,058.662)	67,791.14 (61,588.874, 74,618.012)
	Min, max	9,588.0, 39,077.0	46,686.4, 92,994.9
Fluctuation (%) after fourth infusion	n	20	21
	Geometric mean (95% CI)	140.49 (123.597, 159.690)	117.89 (99.569, 139.583)
	Min, max	82.3, 222.2	55.9, 323.0
Vd (L) after fourth infusion	n	15	12
	Geometric mean (95% CI)	4.66 (3.910, 5.552)	5.11 (4.382, 5.966)
	Min, max	2.2, 8.3	3.8, 7.9
λz after fourth infusion (1/day)	n	15	12
	Geometric mean (95% CI)	0.03 (0.024, 0.034)	0.02 (0.021, 0.028)
	Min, max	0.0, 0.1	0.0, 0.0

$t_{1/2}$ after fourth infusion (day)	n	15	12
	Geometric mean (95% CI)	23.04 (19.865, 26.726)	28.02 (24.344, 32.243)
	Min, max	13.9, 33.0	17.0, 37.5

λz=terminal rate constant; AI (expected)=expected accumulation index; AUC_{0-inf}=area under the serum concentration-time curve extrapolated to infinity; AUC_{extrap}(%)=area under the serum concentration-time curve percentage extrapolated area; C_{avg}=average concentration; CI=confidence interval; CL=clearance; max=maximum; min=minimum; PK=pharmacokinetic(s); $t_{1/2}$=apparent terminal half-life; Vd=apparent volume of distribution

Anti-KY1005 Antibody Titer and Number of Patients with Positive Response

Main Study (to Day 113):

The number and percentage of patients with a positive and negative ADA response is summarized in Table 18 (Safety Set).

Table 18: Presence of Anti-KY1005 Antibodies (Safety Set) (Main Study)

		KY1005 Low Dose	KY1005 High Dose	Placebo
Baseline	n	29	30	29
	Negative	28 (96.6%)	30 (100.0%)	26 (89.7%)
	Positive	1 (3.4%)	0 (0.0%)	3 (10.3%)
Day 15	n	28	27	26
	Negative	24 (85.7%)	26 (96.3%)	24 (92.3%)
	Positive	4 (14.3%)	1 (3.7%)	2 (7.7%)
Day 29	n	26	27	24
	Negative	22 (84.6%)	26 (96.3%)	22 (91.7%)
	Positive	4 (15.4%)	1 (3.7%)	2 (8.3%)
Day 57	n	24	23	19
	Negative	15 (62.5%)	23 (100.0%)	17 (89.5%)
	Positive	9 (37.5%)	0 (0.0%)	2 (10.5%)
Day 85	n	22	23	18
	Negative	13 (59.1%)	23 (100.0%)	16 (88.9%)
	Positive	9 (40.9%)	0 (0.0%)	2 (11.1%)
Day 113	n	20	22	16
	Negative	10 (50.0%)	22 (100.0%)	14 (87.5%)
	Positive	10 (50.0%)	0 (0.0%)	2 (12.5%)
Early termination – Main study	n	2	4	10
	Negative	2 (100.0%)	3 (75.0%)	8 (80.0%)
	Positive	0 (0.0%)	1 (25.0%)	2 (20.0%)

Note: Positive represents a titre result ≥1.

The presence and endpoint titer of anti-KY1005 ADAs were determined using a solid-phase extraction acid dissociation bioanalytical method with high estimated sensitivity (5.5 ng/mL) and high tolerance to on-board KY1005 drug concentrations (55 ng/mL and 9 ng/mL ADA positive control tolerated up to 100 and 10 µg/mL KY1005, respectively.)

For the Safety Set, anti-KY1005 antibodies (i.e., titer result ≥1) were detected at baseline for one patient (3.4%) in the KY1005 low dose group (titer of 34.3) and no patients in the KY1005 high dose group (Table 18.) A positive result was also reported at Baseline for three patients (10.3%) in the placebo group, but the recorded titers were low. Anti-KY1005 antibodies were detected in increasing numbers of patients in the KY1005 low dose group over time, while patients in the KY1005 high dose and placebo groups were generally negative. By Day 113, of the patients with available ADA data, anti-KY1005 antibodies were detected for 10 patients (50.0%) in the KY1005 low dose group and no patient in the KY1005 high dose group. For the 10 patients in the KY1005 low dose group with a positive ADA result, the median titer was 11.85 (range: 1.6 to 465.0). A positive result was also reported at Day 113 for two patients (12.5%) in the placebo group, but the recorded titers were low (3.1 and 3.4). No unexpected changes in PK profile were observed in patients with positive ADA. Given that the bioanalytical PK assay format ensured measurement of active drug (i.e., unbound to OX40L), these findings indicated that where present, ADAs were likely to be weakly or non-neutralizing. No adverse events were associated with positive ADA.

Study Extension (from Day 113):

The number and percentage of responders with a positive and negative response is summarized in Table 19. Similar to the trend in the main study, anti-KY1005 antibodies were detected in increasing numbers of responders in the KY1005 low dose group over time, while those in the KY1005 high dose and placebo groups were negative.

At Day 113, of the responders with available ADA data, anti-KY1005 antibodies were detected for 6 patients (50%) in the KY1005 low dose group with a median titer of 7.94 (range: 1.7 to 29.4). By Day 253, 9 out of 11 patients (81.8%) in the KY1005 low dose group were positive for anti-KY1005 antibodies with a median titer of 53.50 (range: 1.5 to 1740).

As observed in the main study, no unexpected changes in the PK profile were observed in patients with a positive ADA result, although the expected low serum concentrations of KY1005 at Day 253 did not aid interpretation at the final timepoint in this regard. No adverse events were associated with positive ADA.

Table 19: Presence of Anti-KY1005 Antibodies (Responders) (Study Extension)

		KY1005 Low Dose	KY1005 High Dose	Placebo
	n	12	10	2
	Negative	6 (50%)	10 (100.0%)	2 (100.0%)

Day 113	Positive	6 (50%)	0 (0.0%)	0 (0.0%)
Day 169	n	12	10	2
	Negative	3 (25.0%)	10 (100.0%)	2 (100.0%)
	Positive	9 (75.0%)	0 (0.0%)	0 (0.0%)
Day 253	n	11	8	2
	Negative	2 (18.2%)	8 (100.0%)	2 (100.0%)
	Positive	9 (81.8%)	0 (0.0%)	0 (0.0%)

Note: Positive represents a titre result ≥1.

Efficacy and Other Evaluations Conclusions

Main Study to Day 113:

Improvements from baseline were observed in the FAS for the primary efficacy endpoint (percentage change in EASI from Baseline to Day 113), with larger reductions observed in the KY1005 treatment groups compared to placebo. The difference versus placebo was nominally statistically significant for the KY1005 low dose group (p=0.009) but not for the high dose group (p=0.072) at Day 113. Treatment differences were observed with both KY1005 low and high dose groups as early as Day 15 vs placebo and maintained to Day 113. Repeat of the primary efficacy analysis for the PPS and for the sensitivity analyses (using EASI stratum as covariate; with rescue medication within the first month and rescue medication-by-treatment as fixed effects) provided similar results to the main analysis.

Nominally statistically significant improvements from baseline in both KY1005 groups compared to placebo were also observed for the following secondary efficacy endpoints vIGA, SCORAD Index, and affected BSA. There were generally no clear differences between the KY1005 low and high dose groups in either the speed of onset or magnitude of responses.

While reductions from Baseline were generally observed for the secondary patient reported outcome efficacy endpoints of POEM total score, and DLQI total score, these were apparent across all treatment groups, including placebo, and there were no clear differences between the groups. The exception however, was the PO-SCORAD, which demonstrated a nominally statistically significant difference for the KY1005 low dose group compared with placebo.

For patients with a baseline NRS of at least 3 and at least 4, the percentage of patients with a best improvement in NRS for pruritus of at least 3 units and at least 4 units, respectively, was higher in the KY1005 high dose group compared to the KY1005 low dose group and the placebo group.

Results for the subgroup of patients in the EASI >21 stratum (severe disease – 56 patients) were similar to those observed in the FAS. Results for the EAST ≤21 stratum (moderate disease – 22 patients) were also generally similar to those observed in the FAS, but the low numbers of patients

included in this stratum makes it difficult to draw meaningful conclusions as to whether Baseline disease severity has a meaningful impact on response.

Pharmacokinetics

C_{max}, AUC_{0-28} and AUC_{0-inf} appeared to be approximately dose proportional, and peak concentrations (45 minutes after the start of all infusions) did not appear to increase on repeat dosing. AUC_{0-28} and C_{min} (trough) levels were similar when first (loading) and fourth (third maintenance) dose exposures were compared and there was minimal accumulation after administration of four doses every 28 days.

Serum concentrations of KY1005 increased rapidly following dosing, with a median t_{max} of 0.03 days for both the KY1005 low and high doses. Following each dose, serum concentrations steadily decreased in a biphasic manner. No target mediated drug disposition was apparent.

In general, the mean serum concentration profile for KY1005 was dose proportional, where the 2.5-fold increase in dose attained an approximately 2.5-fold increase in exposure as measured by C_{max} and AUC_{0-28}.

Pharmacodynamics

Anti-KY1005 antibodies were detected in increasing numbers of patients in the KY1005 low dose group over time, while patients in the KY1005 high dose and placebo groups were generally negative. By Day 113 in patients with available data, anti-KY1005 antibodies were detected for 10 patients (50.0%) in the KY1005 low dose group and no patient in the KY1005 high dose group. For the 10 patients in the KY1005 low dose group with a positive ADA result, the median titer was 11.85 (range: 1.6 to 465.0).

No unexpected changes in PK profile was observed in patients with positive ADA, indicating that where present, ADAs were likely to be weakly or non-neutralizing.

Study Extension

Efficacy

A total of 24 patients were defined as responders (vIGA 0/1) at Day 113 (12, 10 and 2 patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively). On average, improvements from baseline were generally sustained throughout the study extension (to Day 253) in this subset of patients across the exploratory endpoints of EASI, vIGA, SCORAD Index, affected BSA, POEM total score, PO-SCORAD Index, DLQI and NRS for pruritus. However, interpretation is difficult, particularly in the placebo group where there were only 2 patients.

Pharmacokinetics

Serum concentrations of KY1005 steadily decreased from Day 113 to the end of study, with an approximately dose proportional relationship observed for $AUC_{0\text{-inf.}}$ Similar accumulation index calculated after the fourth dose (about 2-fold), and Vd (about 5 L) was observed for the two KY1005 dose groups, and no target mediated drug disposition was apparent. Geometric mean t1/2 values were similar for the low (23.04 days) and high (28.02 days) dose groups.

Pharmacodynamics

Anti-KY1005 antibodies were increasingly detected in the KY1005 low dose group over time, while patients in the KY1005 high dose and placebo groups were negative. By Day 253, of those patients who were defined as responders (vIGA 0/1) at Day 113, 9 out of 11 patients (81.8%) in the KY1005 low dose group were positive for anti-KY1005 antibodies with a median titer of 53.50 (range: 1.5 to 1740).

Adverse Events

During the main study (prior to Visit 19), similar numbers of patients experienced at least one TEAE in the KY1005 low dose and placebo groups (18 [62.1%] and 20 [69.0%] patients, respectively), whereas the number was lower in the KY1005 high dose group (14 [46.7%] patients). Likewise, treatment-related TEAEs were reported for similar numbers of patients in the KY1005 low dose and placebo groups (10 [34.5%] and nine [31.0%] patients, respectively), but a lower number in the KY1005 high dose group (six [20.0%] patients).

One patient (3.4%) in the KY1005 low dose group experienced a serious TEAE during the main study, which was considered treatment-related, and one patient (3.3%) in the KY1005 high dose group experienced a treatment-emergent AESI, which was considered unrelated to treatment. Treatment-emergent AEs leading to discontinuation of study treatment were reported for three patients, including two patients in the placebo group and one patient in the KY1005 low dose group during the main study.

For the study extension, percentages were calculated based on the patients who performed at least one visit of the extension study. During the study extension (from Visit 19), similar numbers of patients experienced at least one TEAE in the KY1005 high dose and low dose groups (seven [35.0%] and eight [36.4%] patients, respectively), whereas the number was lower in the placebo group (four [23.5%] patients). Treatment-related TEAEs were reported for two (10.0%) patients in the KY1005 low dose group and no patients in the KY1005 high dose and placebo groups. One patient (5.0%) in the KY1005 low dose group experienced a serious TEAE during the study extension, which was

considered unrelated to study treatment. One patient (5.0%) in the KY1005 low dose group experienced a treatment-emergent AESI, which was considered unrelated to study treatment.

At the discretion of the Investigator, patients could be rescued with a prohibited medication or procedure for the treatment of intolerable AD symptoms. Within the first month from Baseline, up to two rescue therapy administrations of up to 3 days with topical therapies were permitted without permanent discontinuation of threatment. Use of any rescue therapies was recorded in the eCRF. Patients who received any systemic rescue treatment with a prohibited medication or procedure from Baseline through Day 113 were to be permanently discontinued from treatment.

Rescue medications within the first month included corticosteroids, dermatological Preparations, administered to three patients in each of the three treatment groups, and other dermatological preparations, administered to one patient in the KY1005 high dose group (Table 20.)

Table 20: Summary of Rescue Medications within the First Month Tabulated by ATC Level 2 Group and WHO Preferred Name (SAF)

ATC Level 2 Group Text	WHO preferred name	KY1005 low dose (n=29)	KY1005 high dose (n=30)	Placebo (n=29)
Corticosteroids.	Total	3 (10.3%)	3 (10.0%)	3 (10.3%)
Dermatological Preparations	Betamethasone dipropionate	0 (0.0%)	0 (0.0%)	1 (3.4%)
	Betamethasone dipropionate:Gentamicin sulfate	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Clobetasol propionate	1 (3.4%)	1 (3.3%)	0 (0.0%)
	Dexamethasone	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Methylprednisolone	0 (0.0%)	0 (0.0%)	1 (3.4%)
	Methylprednisolone aceponate	0 (0.0%)	0 (0.0%)	1 (3.4%)
	Mometasone furoate	2 (6.9%)	2 (6.7%)	1 (3.4%)
Other Dermatological Preparations	Total	0 (0.0%)	1 (3.3%)	0 (0.0%)
	Tacrolimus	0 (0.0%)	1 (3.3%)	0 (0.0%)

Rescue Medication: 'During the BDRM it will also be decided which medications will be counted as rescue medications. Coding: WHO Drug Dictionary Enhanced. 01 SEP 2018

Conclusions

This Phase IIa, randomized, double-blind, placebo-controlled, parallel group, multicenter study explored the efficacy and safety of KY1005 in adult patients with moderate to severe AD who had a documented history, within 6 months prior to baseline, of either inadequate response to topical treatments or inadvisability of topical treatments. Patients randomized to KY1005 received a loading dose of 500 mg or 200 mg KY1005 followed by three maintenance doses at 50% of the

loading dose at 28-day intervals. Patients randomized to the placebo group received four infusions of matching placebo on Days 1, 29, 57 and 85.

A total of 89 patients were randomized in the study, 59 of whom completed the main study (up to Day 113). One patient in the placebo group terminated the study early due to a protocol deviation prior to the administration of treatment. Three patients terminated the study early due to AEs, all of whom were in the placebo group. The remaining reasons for early termination were withdrawal of consent, 'Other' reasons and failure to meet randomization criteria.

Baseline disease characteristics were as expected for a population of patients with moderate to severe AD and were generally well matched across the treatment groups. While the number of patients in the FAS with a vIGA score of 4 (severe) was higher in the placebo group (15 [62.5%]) compared to the KY1005 groups (10 [37.0] and 9 [33.3%] in the low and high dose groups, respectively), there were no other notable differences between treatment groups in baseline disease characteristics, including affected BSA, EASI, SCORAD, and NRS for pruritus.

The primary efficacy endpoint was the percentage change in EASI from Baseline to Day 113. Progressive reductions in EASI score from Baseline to Days 15, 29, 57, 85 and 113 in the FAS were observed across all treatment groups, including placebo. However, greater reductions were observed in the KY1005 groups compared to placebo at all time points. For the Day 113 time point, LSM percentage change (95% CI) from Baseline was -80.12 [-95.55, -64.68] and -69.97 [-85.04, -54.60] for the KY1005 low and high dose groups, respectively, compared to -49.37 [-66.02, -32.72] for placebo. The difference versus placebo was nominally statistically significant for the KY1005 low dose group (p=0.009) but not for the high dose group (p=0.072). Repeat of the primary efficacy analysis for the PPS and for the sensitivity analysis (using EASI stratum as covariate; with rescue mediation within the first month and rescue medication-by-treatment as fixed effects) provided similar result to the main analysis.

Nominally statistically significant improvements from Baseline in both KY1005 groups compared to placebo were also observed for the following secondary efficacy endpoints vIGA, SCORAD Index, and affected BSA. There were generally no clear differences between the KY1005 low and high dose groups in either the speed of onset or magnitude of responses.

While reductions from Baseline were generally observed for the secondary patient reported outcome efficacy endpoints of POEM total score and DLQI total score, these were apparent across all treatment groups, including placebo, and there were no clear differences between the groups. The exception however, was the PO-SCORAD, which demonstrated a nominally statistically significant difference for the KY1005 low dose group compared with placebo.

For patients with a Baseline NRS of at least 3 and at least 4, the percentage of patients with a best improvement in NRS for pruritus of at least 3 units and at least 4 units, respectively was higher in the KY1005 groups compared with the placebo group.

Results for the subgroup of patients in the EASI >21 stratum (severe disease – 56 patients) were similar to those observed in the FAS. Results for the EAST ≤21 stratum (moderate disease – 22 patients) were also generally similar to those observed in the FAS, but the low numbers of patients included in this stratum makes it difficult to draw meaningful conclusions as to whether Baseline disease severity has a meaningful impact on response.

A total of 24 patients were defined as responders (vIGA 0/1) at Day 113 (12, 10 and 2 patients in the KY1005 low dose, KY1005 high dose and placebo groups, respectively). On average, improvements from Baseline were generally sustained throughout the study extension (to Day 253) in this subset of patients across the exploratory endpoints of EASI, vIGA, SCORAD Index, affected BSA, POEM total score, PO-SCORAD Index, DLQI and NRS for pruritus. However, where differences were observed it is not possible to determine whether this is due to a true treatment effect or due to the low numbers of patients and the widely overlapping 95% CIs.

Clinically meaningful improvements from Baseline in the KY1005 groups compared to placebo were observed for the majority of the efficacy endpoints, including the primary endpoint (percentage change in EASI from Baseline to Day 113) and the secondary efficacy endpoints of EASI 50, EASI 75 and EASI 90, vIGA, SCORAD Index, affected BSA and PO-SCORAD Index. The differences versus placebo were nominally statistically significant for the KY1005 low dose group for the primary endpoint and PO-SCORAD, and for both KY1005 groups for vIGA, SCORAD, and affected BSA.

Consistent with previous observations, evaluation of PK revealed that serum concentrations of KY1005 increased rapidly following I.V. administration, with a median t_{max} of 0.03 days and an approximately dose proportional relationship for C_{max}, $AUC_{0\text{-}28}$ and $AUC_{0\text{-}inf.}$ Following each dose, serum concentrations steadily decreased in a biphasic manner, with estimated $t_{1/2}$ values that were similar for the low and high doses. No target-mediated drug disposition was apparent and there was minimal accumulation after administration of four doses every 28 days. KY1005 was still measurable in serum at 168 days after the final dose, even at the low dose level.

KY1005 was well tolerated following I.V. administration of 500 mg and 200 mg loading doses followed by three maintenance (50%) doses, with no safety concerns identified in this study.

Anti-KY1005 antibodies were detected in increasing numbers of patients in the KY1005 low dose group over time, while patients in the KY1005 high dose and placebo groups were generally negative. By Day 113 in patients with available data, anti-KY1005 antibodies were detected for 10 patients (50.0%) in the KY1005 low dose group and no patient in the KY1005 high dose group. For the 10 patients in the KY1005 low dose group with a positive ADA result, the median titer was 11.85 (range: 1.6 to 465.0). By Day 253, of those patients who were defined as responders (vIGA 0/1) at Day 113, 9 out of 11 patients (81.8%) in the KY1005 low dose group were positive for anti-KY1005 antibodies with a median titer of 53.50 (range: 1.5 to 1740). No unexpected changes in PK profile was observed in patients with positive ADA, indicating that where present,

ADAs were likely to be weakly or non-neutralizing. No adverse events were associated with positive ADA.

Repeat dosing of KY1005 was well tolerated during the main study (up to Day 113) and study extension (up to Day 253), with no safety concerns identified in this study. Overall, there were no clear trends in the numbers of patients reporting TEAEs and treatment-related TEAEs, by SOC and PT.

No deaths occurred during the study up to Day 113. One serious TEAE was reported up to Day 113: an event of Infected dermal cyst in a patient in the KY1005 low dose group. This event was considered possibly related to treatment, although the case was confounded by the patient's ongoing medical history of dermal cysts. One treatment-emergent AESI was reported during the study up to Day 113 and one was reported during the study extension post-Day 113. Both events were considered unrelated to treatment. One serious TEAE of 'sudden death' was reported post-Day 113 on study Day 172 (3 months after last of dose of KY1005 low dose); this event was considered unrelated by the investigator.

Treatment-emergent AEs leading to discontinuation (of study treatment and/or the study overall) were reported for four patients. The events in these cases were reflective of exacerbation of the underlying disease leading to withdrawal (two patients; placebo), a report of Drug ineffective leading to withdrawal (placebo) and a mild event of Nasopharyngitis leading to treatment discontinuation (KY1005 low dose).

No clinically relevant trends in clinical laboratory parameters were observed following treatment with KY1005 or placebo, and no safety concerns were raised. Treatment-emergent AEs in the System Organ Class (SOC) of Investigations were reported for broadly similar numbers of patients across the treatment groups. These abnormalities were sporadic findings and there were no clear trends related to treatment. There were no clinically meaningful changes from baseline or differences between treatment groups in vital signs and ECG measurements.

In the study extension, on average improvements from baseline were generally sustained throughout the study extension (to Day 253) in responders (vIGA 0/1 at Day 113) across the exploratory endpoints of EASI, vIGA, SCORAD Index, affected BSA, POEM total score, PO-SCORAD Index, DLQI and NRS for pruritus. KY1005 continued to be well tolerated during follow-up in the study extension (up to Day 253), with no safety concerns identified in this study. The PK profile of KY1005 was as expected in the study extension, and the geometric mean $t_{1/2}$ ranged from 23 to 28 days. KY1005 was still measurable in serum 168 days after the final dose, even at the low dose level.

Example 3: A Phase I, Open-label Study to Assess the Pharmacokinetics of KY1005 after Single Dose Administration by Subcutaneous and Intravenous Route in Healthy Volunteers, ClinicalTrials.gov Identifier: NCT04449939 (KY1005-CT04)

Primary Objective

To assess the pharmacokinetics (PK) of KY1005 when administered subcutaneously.

Secondary Objectives

To assess the safety & tolerability of KY1005 when administered subcutaneously and intravenously.

To assess the immunogenicity of KY1005.

Primary Endpoints

The following PK parameters of KY1005 after I.V. and S.C. administration were assessed: maximum observed concentration after I.V. or S.C. administration (C_{max}); time at which C_{max} is observed (t_{max}); area under the concentration time curve from time 0 to last observation (AUC_{last}); area under the concentration time curve from time 0 to infinity (AUC_{inf}); percentage of AUC_{inf} extrapolated from t_{last} to infinity ($\%AUC_{extrap}$); mean residence time (MRT_{inf}); systemic clearance after I.V. infusion (CL); apparent systemic clearance after S.C. injection (CL/F); volume of distribution during the terminal phase after I.V. infusion (V_z); apparent volume of distribution after S.C. injection (V_z/F); steady-state volume of distribution after I.V. infusion (Vss); weight-normalised Vss and V_z; half-life ($t_{1/2}$); and terminal rate constant (λ_z), dose-normalised C_{max} (C_{max}/D) and dose-normalised AUC_{inf} (AUC_{inf}/D) following SC and IV administration, and absolute bioavailability (F) calculated as the ratio of AUC_{inf}/D after I.V. and S.C. administration.

Secondary endpoints

Incidence of TEAEs, treatment-emergent serious adverse events (TESAEs) and local injection site reactions.

Vital signs, laboratory safety tests, 12-lead ECG, physical examination.

Anti-KY1005 antibody titer and number of subjects with positive response.

Study Design

This was a Phase 1, single-center, open-label, parallel-group, single-dose study to assess the PK, safety and tolerability of KY1005 after S.C. and I.V. administration in healthy male volunteers. KY1005 administered I.V.was defined as the reference treatment. A schematic diagram of the study design is presented in **FIG. 15**.

Dosage and evaluation groups

Three groups of 8 healthy men were enrolled into the study (Groups 1–3). Subjects for Groups 2 and 3 were recruited before those for Group 1. Each subject had 1 study session in which they received a single dose of KY1005 via S.C. injection(s) or I.V. infusion, as follows.

Comparator Group 1: single dose of 250 mg KY1005, given by I.V. infusion over 30 min followed by saline flush over 15 min.

Group 2: single dose of 125 mg (1 mL) KY1005, given by S.C. injection into the abdomen.

Group 3: single dose of 250 mg (2 mL) KY1005, given as sequential 2 × 1 mL S.C. injections into the abdomen.

As KY1005 had not been administered to humans by S.C. injection before; there were at least 7 days between dosing of Groups 2 and 3.

Study visits

All subjects were screened within 28 days before their dose of KY1005.

All subjects received a single dose of KY1005 on Day 1. Subjects who received KY1005 by I.V. infusion (Group 1) were resident on ward from the day before their dose (Day –1) until 24 h after dosing (Day 2). Subjects who received KY1005 by S.C. injection (Groups 2 and 3) were resident on ward from the day before their dose (Day –1) until 96 h after dosing (Day 5). All subjects returned to the ward for 7 outpatient visits after their dose, on Days 8, 15, 22, 29, 36, 57 and 78. They also attended a follow-up visit at about 91 days after their dose (Day 92 ± 2 days). The end of the trial was defined as the last visit by the last subject.

Study Assessments

The following assessments were made:

Pharmacokinetic: blood samples for assay of KY1005 were taken before and at frequent time points up to 24 h after dosing (Days 1–2); each morning on Days 3–5 (Groups 2 and 3 only); at each outpatient visit (Days 15–78); and at the final follow-up visit (Day 92).

Safety: laboratory assessments (routine hematology, biochemistry, and urinalysis), physical examination, 12-lead ECG, vital signs, local tolerability, and AEs.

Tolerability: AEs.

Immunogenicity: blood samples for assay of ADA were taken before dosing and at multiple timepoints throughout the study.

Inclusion criteria

Subjects were eligible for inclusion in the trial if they met the following criteria:

1. Healthy male volunteer, aged 18–45 years at screening (i.e. the time of informed consent).
2. Body weight 60–120 kg, and a body mass index (BMI; Quetelet index) in the range 18.0–30.0 kg/m^2 (inclusive).

(Other Inclusion and Exclusion Criteria available online at ClinicalTrials.gov, Identifier: NCT04449939)

Treatments administered

The dosing schedule is presented in Table 21.

Table 21: Dosing Schedule

Group	Investigational Medicinal Product	Dose	Route of Administration	Frequency and/or Regime
1	KY1005	250 mg	IV	Single dose
2	KY1005	125 mg	SC	Single dose
3	KY1005	250 mg	SC	Single dose given as two 125 mg administrations

Subjects in Group 1 received a single dose of KY1005 as an I.V. infusion of about 100 mL (250 mg KY1005 in sterile 0.9% saline) over 30 min into a forearm vein, followed by a saline flush over 15 min.

Subjects in Groups 2 and 3 received a single dose of KY1005 by S.C. injection. Subjects in Group 2 received an injection of 1 mL (125 mg KY1005) and subjects in Group 3 received 2 sequential injections of 1 mL each (250 mg KY1005 in total) into the abdomen, given 20–60 min apart.

Identity of test product

KY1005 was formulated as a liquid at 125 mg/mL KY1005.

KY1005 was aseptically filled into 2 mL Type 1 clear glass vials with a nominal fill volume of 1 mL, sealed with FluoroTec coated stoppers and crimped with overcaps to ensure container closure integrity. The recommended storage temperature was 2–8°C.

Serum pharmacokinetics

The concentration of KY1005 in all predose samples was below the limit of quantification (BLQ) (lower limit of quantification (LLQ) was 46.9 ng/mL).

Mean serum concentrations are summarized in Table 22. Mean serum concentrations are plotted against time in **FIG. 16A** (linear) and **FIG. 16B** (semi-logarithmic) and **FIG. 17A** (linear) and **FIG. 17B** (semi-logarithmic).

Table 22: KY1005 serum concentrations after single intravenous and subcutaneous doses of KY1005: PK concentration population (n=8 per group)

Study day	Nominal post-dose timepoint (h)	Arithmetic mean (SD) serum concentrations of KY1005 (ng/mL)					
		250 mg KY1005 IV (N=8)		250 mg KY1005 SC (N=8)		125 mg KY1005 SC (N=8)	
1	Predose	08	--	08	--	08	--
	End of infusion*	88931.34	(17383.91)	--	--	--	--
	1	87854.54	(14278.25)	276.79	(257.837)	40.693	(36.480)
	2	83639.46	(9867.235)	699.91	(408.109)	270.581	(196.077)
	4	84028.64	(11227.33)	1744.94	(666.527)	1054.14	(713.555)
	8	80799.99	(11512.26)	4455.90	(1695.732)	2414.64	(1540.815)
	12	71815.49	(11502.46)	6365.51	(2445.451)	3824.13	(2173.649)
2	24	65446.84	(9615.421)	9640.45	(3656.326)	6009.41	(3049.784)
	48	--	--	16524.50	(6769.445)	10197.54	(3741.174)
4	72	--	--	19988.15	(6364.779)	11409.30	(3279.915)
5	96	--	--	21833.04	(6779.306)	12541.60	(3544.389)
8	168	36846.09	(5063.785)	25802.99	(4265.096)	14222.35	(2309.279)
15	--	31773.21	(3467.040)	24750.85	(4098.516)	13965.35	(2664.434)
22	--	28372.71	(4803.550)	22544.18	(3854.234)	12336.64	(1799.133)
29	--	22414.00	(4822.714)	19264.55	(3953.609)	11243.12	(1784.189)
36	--	20277.83	(2947.633)	19584.08	(3093.818)	10182.74	(1377.499)
57	--	13714.40	(3905.523)	12729.15	(2723.015)	6671.20	(1046.571)
78	--	9267.16	(2170.903)	9784.15	(2004.073)	4354.85	(999.288)
92	Follow-up	7162.31	(3152.584)	7748.31	(2720.715)	3215.93	(1036.034)

* I.V. dosing only. N: number of subjects receiving treatment; SD: standard deviation; Numerical superscripts indicate the number of imputed values.

As shown in **FIG. 17A** (linear) and **FIG. 17B** (semi-logarithmic), single 250 mg KY1005 I.V. doses rapidly achieved peak serum concentrations at the end of infusion (30 min): mean serum concentration was 88,931 ng/mL; individual subject concentrations at end-infusion ranged from 72,391 to 120,333 ng/mL (with a 1.66 fold ratio between subjects at each extreme). There was high variation in t_{max}, which ranged from 0.77 to 8.93 h; 3 subjects (1001, 1004 and 1005) had t_{max} of 8.8, 8.9 and 4.8 h, respectively.

As shown in **FIG. 16A** (linear) and **FIG. 16B** (semi-logarithmic), 250 mg KY1005 I.V. showed biphasic elimination. A rapid phase occurred between end of infusion (Day 1) and 168 h (Day 8) after dosing, during which time the mean serum concentration fell from 65,447 to 36,846 ng/mL. That was followed by a slower terminal elimination phase in the rest of the sampling period.

Absorption *via* the S.C. route was slower than seen for the I.V. administered drug: mean serum concentration peaked at 168 h post dose (Day 8) after both 250 mg KY1005 (25,803 ng/mL) and 125 mg (14,222 ng/mL) S.C. doses. From Day 8 onwards, t_{max} was constrained by 7 to 21-day sampling intervals, which may have contributed to the substantial variation in t_{max} after S.C. dosing: individual t_{max} ranged from 96 (Day 4) to 336 h (Day 15), and 96 (Day 4) to 504 h (Day 22), after 250 mg and 125 mg S.C., respectively; median t_{max} was at the 168-h (Day 8) timepoint.

Mean serum concentration after 250 mg I.V. and S.C. doses converged at about 20,000 ng/mL on Day 36. After that point, mean serum–concentration time curves for both regimens were closely similar throughout the rest of the sampling period, both falling to about 7,000 ng/mL at Follow-up (Day 92). The mean serum-concentration time curve after 125 mg S.C. was similar in profile to that after 250 mg S.C. doses, albeit at about half the concentration.

Serum parameters

Selected PK parameters of KY1005 are summarized in Table 23.

Table 23: Summary of KY1005 serum pharmacokinetic parameters after single intravenous and subcutaneous doses of KY1005: PK parameter population (n=8 per group)

KY1005 parameter		250 mg KY1005 I.V. (N=8)	250 mg KY1005 S.C. (N=8)	125 mg KY1005 S.C. (N=8)
C_{max} (ng/mL)	geo mean[a]	90426	26130	15146
	95% CI	(79129, 103336)	(22170, 30798)	(12961, 17700)
	Range	75616–120333	17975–33458	10005–18351
C_{max}/D (ng/mL/g)	geo mean[a]	362	105	121
	95% CI	(317, 413)	(88.7, 123)	(104, 142)
	Range	302–481	71.9–134	80.0–147
t_{max} (h)	Median	1.79	169	170
	Range	0.767–8.93	96.5–337	96.0–504
λZ (1/h)	mean[b]	0.821×10^{-3}	0.632×10^{-3}	0.915×10^{-3}
	SD (%CVb)	0.121×10^{-3} (14.8)	0.140×10^{-3} (22.2)	0.305×10^{-3} (33.4)
	Range	$0.674–0.981 \times 10^{-3}$	$0.455–0.850 \times 10^{-3}$	$0.673–1.611 \times 10^{-3}$
$t_{1/2}$ (h)	mean[b]	861	1145	813
	SD (%CVb)	127 (14.7)	251 (21.9)	194 (23.9)
	Range	706–1028	815–1523	430–1029
AUC_{inf} (mg·h/mL)	geo mean[a]	52.8	46.7	21.9
	95% CI	(45.0, 61.9)	(39.1, 55.9)	(18.4, 26.0)
	Range	42.5–70.2	35.3–73.2	14.7–26.6
AUC_{inf}/D (mg·h/mL/mg)	geo mean[a]	0.21	0.19	0.18
	95% CI	(0.18, 0.25)	(0.16, 0.22)	(0.15, 0.21)
	Range	0.17–0.28	0.14–0.29	0.12–0.21
AUC_{last} (mg·h/mL)	geo mean[a]	44.5	33.9	18.1
	95% CI	(39.4, 50.2)	(29.5, 38.8)	(15.8, 20.7)
	Range	37.7–56.3	26.5–45.5	12.6–20.4
$\%AUC_{extrap}$ (%)	mean[b]	15.6	27.2	17.1
	SD (%CVb)	5.3 (33.9)	8.1 (29.6)	6.1 (35.4)
	Range	7.8–22.1	15.3–37.8	5.7–23.1
MRT_{inf} (h)	geo mean[a]	1178	1674	1275
	95% CI	(1047, 1326)	(1383, 2026)	(1097, 1483)
	Range	1020–1428	1164–2234	896–1515
Vz/F (L)	mean[b]	–	8.78	6.60
	SD (%CVb)	–	1.72 (19.5)	1.28 (19.4)
	mean[b]	5.86	–	–

V_z	SD (%CVb)	0.698 (11.9)	–	–
$V_{z,norm}$ (L/kg)	mean[b]	0.0773	–	–
	SD (%CVb)	0.00991 (12.8)	–	–
Vss (L)	mean[b]	5.61	–	–
	SD (%CVb)	0.624 (11.1)	–	–
$V_{ss,norm}$ (L/kg)	mean[b]	0.0740	–	–
	SD (%CVb)	0.008951 (12.1)	–	–
CL/F (L/h)	mean[b]	–	0.005451	0.005820
	SD (%CVb)	–	0.001061 (19.5)	0.001325 (22.8)
CL (L/h)	mean[b]	0.004807	–	–
	SD (%CVb)	0.000876 (18.2)	–	–

$\%AUC_{extrap}$: percentage of AUC_{inf} extrapolated from last to infinity; %CVb: between-subject coefficient of variance; C_{max}: maximum observed concentration; C_{max}/D: dose-normalised C_{max}; t_{max}: time at which C_{max} is observed; AUC_{0-t}: area under the concentration time curve from time 0 to last observation; AUC_{inf}: area under the concentration time curve from time 0 to infinity; AUC_{inf}/D: dose-normalised AUC_{inf}; CL: systemic clearance after I.V. infusion; CL/F: apparent systemic clearance after S.C. injection; V_z: volume of distribution during the terminal phase after IV infusion; V_z/F: apparent volume of distribution after S.C. injection; V_{ss}: steady-state volume of distribution after I.V. infusion; $V_{ss,norm}$: body weight-normalised V_{ss}; $V_{z,norm}$: body weight- normalised V_z; $t_{1/2}$: terminal elimination half-life; λ_z: terminal elimination rate constant.
a: geometric mean; b: arithmetic mean.

After 250 mg KY1005 I.V., median t_{max} derived using actual sampling times was 1.79 h, though the true peak concentration, consistent with the PK of monoclonal antibodies, must certainly have been at the end of infusion (30 min); and mean C_{max} occurred at this time. Geometric mean C_{max}/D was 362 ng/mg/mL. Absorption of S.C. doses was slow, and yielded lower serum concentrations than did I.V. doses: median t_{max} was 170 and 169 h, and C_{max}/D was 121 and 105 ng/mL/mg, after 125 mg and 250 mg S.C., respectively. Variation in C_{max} was low: there was only a 1.59-fold difference between subjects at each extreme after I.V. doses, and 1.86 and 1.83-fold, respectively, after 125 and 250 mg S.C. doses; %CVb was 16.1–19.9 across dosing groups.

Despite the expected differences between I.V. and S.C. administration, dose normalized AUC differed little among dosing groups: geometric mean AUC_{inf}/D was 0.21, 0.18 and 0.19 mgh/mL/mg after 250 mg KY1005 I.V., 125 mg S.C., and 250 mg S.C., respectively. Those findings indicate that S.C. doses have a high degree of bioavailability (F was 0.83 and 0.89 for 125 and 250 mg doses, respectively). Variation in AUC_{inf} was low: there was a 1.65-fold difference between subjects at each extreme after 250 mg KY1005 I.V., and 1.81 and 2.07-fold after 125 mg and 250 mg S.C., respectively; %CVb was 19.2–21.6 across dosing groups.

C_{max} and AUC were broadly dose-proportional after S.C. administration of KY1005: geometric mean C_{max} was 15,146 and 26,130 ng/mL, AUC_{inf} was 21.9 and 46.7 mgh/mL, and AUC_{last} was 18.1 and 33.9 mg·h/mL, after 125 mg and 250 mg S.C., respectively, equating to 1.7 to 2.1-fold differences in mean between the 2 dosing groups.

Arithmetic mean $t_{1/2}$ was similar for all dose groups, and ranged from 813 to 1145 h. The close fit of the regression line to the λz plots suggests valid estimation of $t_{1/2}$ for all subjects who received KY1005; arithmetic mean $\%AUC_{extrap}$ was 15.6% after 250 mg I.V., 27.2% after 250 mg S.C., and 17.1% after 125 mg S.C.

As with serum concentration, between-subject variation in elimination parameters ($t_{1/2}$ and λ_z) was low: %CVb was about 14.8% after IV doses, and 21.9–33.4% after S.C. doses.

Geometric mean MRT_{inf} was similar after 250 mg KY1005 I.V. and 125 mg S.C. (1178 and 1275 h, respectively) but about 1.3 to 1.4-fold higher (1674 h) after 250 mg S.C.; %CVb was 14.2–22.0 across dosing groups. Those values are similar to the corresponding ones for $t_{1/2}$.

As a result of the differences in dose-normalized AUC, V_z/F and CL/F inevitably differed slightly between S.C. doses: arithmetic mean V_z/F was 6.60 and 8.78 L, and CL/F was 0.00582 and 0.00545 L/h, after 125 and 250 mg KY1005 SC, respectively (%CVb 19.4–22.8). After 250 mg KY1005 I.V., V_z and V_{ss} were 5.86 and 5.61 L, and body weight-normalized $V_{z,norm}$ and $V_{ss,norm}$ were 0.0773 and 0.0740 L/kg, respectively (%CVb 11.1–12.8); CL was 0.00481 L/h (%CVb 18.2).

Absolute bioavailability

Absolute bioavailability of the 2 S.C. dose regimens in the study was assessed for AUC_{inf}/D and is summarized in Table 24.

Table 24: Summary of the absolute bioavailability analysis of single doses of KY1005 given by subcutaneous administration: PK parameter population (n=8 per group)

Parameter	Means			F125	F250
	125 mg KY1005 S.C.	250 mg KY1005 S.C.	250 mg KY1005 I.V.		
AUC_{inf}/D (ng·h/mL/mg)	178268	190966	214740	0.83	0.89

AUC_{inf}/D: dose-normalised area under the concentration time curve from time 0 to infinity; F_{125}: AUC_{inf}/D 125 mg KY1005 S.C. / AUC_{inf}/D 250 mg KY1005 I.V.; F_{250}: AUC_{inf}/D 250 mg KY1005 S.C. / AUC_{inf}/D 250 mg KY1005 I.V.

The absolute bioavailability of KY1005 S.C. doses was similar at each S.C. dose level and was 0.83 after 125 mg S.C. and 0.89 after 250 mg S.C.

Anti-drug antibodies

Serum ADA positive results are summarized in Table 25.

Table 25: Summary of presence of serum anti-drug antibodies (n=8 per group)

Timepoint	250 mg KY1005 I.V. N=8	250 mg KY1005 S.C. N=8	125 mg KY1005 S.C. N=8	All subjects N=24
	n (%)			
Predose	1 (12.5)	2 (25.0)	–	3 (12.5)
Day 8	1 (12.5)	2 (25.0)	2 (25.0)	5 (20.8)
Day 15	1 (12.5)	2 (25.0)	3 (37.5)	6 (25.0)
Day 29	3 (37.5)	3 (37.5)	4 (50.0)	10 (41.7)
Day 57	2 (25.0)	1 (12.5)	4 (50.0)	7 (29.2)
Follow-up	2 (25.0)	3 (37.5)	6 (75.0)	11 (45.8)

1 subject who received 250 mg KY1005 I.V., and 2 subjects who received 250 mg KY1005 S.C., had low titer positive results for ADA before receiving their doses. Measured titers in these subjects remained largely unchanged or reduced during the course of the study. All subjects who received 125 mg KY1005 S.C. had a negative ADA result before dosing.

Prevalence of KY1005 ADA broadly increased with time: in the total population of 24 subjects, ADA were present in 3 subjects (12.5%) before dosing; 5 subjects (20.8%) at Day 8; 6 subjects (25.0%) at Day 15; 10 subjects (41.7%) at Day 29; 7 subjects (29.2%) at Day 57; and 11 subjects (45.8%) at Follow-up (Day 92).

KY1005 ADA were more prevalent after 125 mg KY1005 S.C. than in the 2 other dosing groups: 6 subjects (75.0%) had ADA at Follow-up after 125 mg S.C., compared with 2 (25.0%) and 3 (37.5%) after 250 mg I.V. and S.C., respectively.

Most ADA were of low, single digit titer score. Only 4 subjects, who each received 125 mg KY1005 S.C., had ADA of titer score ≥ 10 at one of their post-dose timepoints, as follows: 3 subjects had a titer score of 20, 10 and 55, respectively, on Day 29 and subject 2007 had a titer score of 87 at follow-up.

No subject who tested positive for ADA had an injection site reaction or a concomitant TEAE. Subject 2007, who had the highest titer score (87 at Follow-up [Day 92], but negative at Day 29), had AUC_{inf} of 14.7 mg·h/mL, the lowest in the dosing group, and about 33% lower than the geometric mean) but his $t_{1/2}$ (719 h) was unremarkable. One subject, who had the second-highest titer score (55 at Day 29, dropping to 2 at Day 57 and < 1 at Follow-up [Day 92]), had the second-lowest AUC_{inf} (17.4 mg·h/mL; about 21% lower than the mean) and the shortest $t_{1/2}$ (430 h; about 47% lower than the mean) in the dosing group.

Conclusions

Pharmacokinetics

KY1005 serum concentration peaked at the end of infusion (30 min) with 250 mg I.V., which is consistent with the I.V. infusion of any drug. However, there was high between-subject variation in t_{max} after 250 mg KY1005 I.V., resulting in mean and median t_{max} of 3.55 and 1.79 h, respectively.

Serum concentrations of a monoclonal antibody would be expected to fall slowly but progressively after the end of an I.V. infusion. For example, mean serum KY1005 concentrations fell by no more than 5.5% from the end of infusion to 4 h post-dose. Without intending to be bound by scientific theory, observed within-subject variation in serum concentrations may reflect the imprecision of the analytical method rather than true variation in t_{max}.

There was biphasic elimination of 250 mg KY1005 I.V.: a rapid phase occurred from 1 to 7 days after dosing, followed by a slower terminal phase.

Absorption *via* the S.C. route was slower than the I.V. route: mean serum concentration peaked at 168 h post-dose (Day 8) after both 125 mg KY1005 and 250 mg S.C.; there was substantial variation in individual-subject t_{max}. Without intending to be bound by scientific theory, this was probably owing to the 7 to 21-day sampling intervals used after Day 8. Dose-normalized C_{max} was about 3 to 3.5-fold higher after 250 mg I.V. than after 250 and 125 mg KY1005 S.C. However, despite those differences, attributable to the different routes of administration, dose normalized absolute bioavailability differed little across dosing groups: 125 and 250 mg KY1005 S.C. yielded 83 and 89% of the AUC_{inf}/D of the 250 mg I.V. dose, respectively.

C_{max} and AUC were broadly dose proportional after KY1005 S.C. administration. Between-subject variability in KY1005 serum concentration was low, as judged by C_{max} and AUC: %CVb was 16.1–21.6 across dosing groups.

Mean serum concentration–time curves showed that elimination of KY1005 after both the I.V. and S.C. dosing was consistent with that expected of a monoclonal antibody. Estimation of $t_{1/2}$ after S.C. doses was good, and variation was low across all dosing groups. Mean $t_{1/2}$ was broadly similar in all dose groups (ranging from 813 to 1145 h). One subject (125 mg KY1005 S.C.) had shorter $t_{1/2}$ (430 h) than did the rest of his dosing group (mean 813 h), which may be consistent with a largely transient ADA response (titre score 55) seen at Day 29. ADA were close to zero however at Day 57 (titre score 2) and 92 (titre score < 1) in this individual.

Safety and tolerability

A secondary objective of the study was to assess the safety and tolerability of KY1005 when administered S.C. and I.V. There were no deaths, SAEs, otherwise significant AEs, or TEAEs leading to withdrawal during the study. All TEAEs were mild or moderate in severity. 250 mg KY1005 I.V. was well tolerated: no subject who received an I.V. dose had a TEAE.

Pharmacodynamics

A secondary objective of the study was to assess the immunogenicity of KY1005.

Prevalence of KY1005 ADAs broadly increased with time, with > 40% of subjects across dosing groups testing positive at Day 29 and Follow-up. ADA were most prevalent in the 125 mg KY1005 S.C. dosing group, particularly at Follow-up (Day 92), when 75.0% of subjects tested positive compared with 25.0% and 37.5% after 250 mg I.V. and S.C., respectively. Overall, ADA were more prevalent in the S.C. than I.V. groups.

Most ADA titer scores were low (single digit titers). PK may have been affected by the presence of ADA in 1 subject (125 mg KY1005) who had a titer score of 55 on Day 29 and low $t_{1/2}$ compared with the rest of their dosing group. No subject who tested positive for ADA had an injection site reaction or concomitant TEAE. However, as the sample size in the present study was small, any effect of ADA on the safety, tolerability and PK of KY1005 should be further elucidated in larger studies.

Example 4: Population PK Analysis Study

A population PK analysis, conducted based on data from the first in human (FIH, CT-01, Example 1 hereinabove) study suggested that for dose levels of >=0.15 mg/kg a linear 2-compartmental distribution model was adequate to describe the signature of the observed data. At lower dose levels (0.006 mg/kg - 0.05 mg/kg), a saturable elimination term needed to be included into the model to describe the distribution and elimination at low dose levels. The underlying reason of this non-linearity at low doses has its source in the fact that the PK assay measures free antibody rather than total antibody concentration and that the initial apparent elimination of the antibody, when administered at very low doses, is due to binding to its target.

A Phase 2a study (KY1005-CT02, as described in Example 2 above) was conducted in patients with moderate to severe atopic dermatitis and a Phase 1 open-label study was conducted in healthy volunteers (KY1005-CT04, as described in Example 3 above). The present analysis was conducted to characterize the pharmacokinetic in healthy volunteers and atopic dermatitis patients, including the absolute bioavailability for subcutaneous administration. A population pharmacokinetic model was developed to support the dose selection in the upcoming Phase IIb study by simulations.

All studies considered in the population PK analysis are listed in Table 26.

Table 26: Overview of the studies included in the population PK analysis

Study	Indication	Route	Regimen	Dose*	Subjects
NCT03161288 (KY1005-CT01 Example 1 above)	Healthy Volunteer	Intravenous	Once every 4 weeks (Q4W)	0.15 mg/kg	6
				0.45 mg/kg	6
				1.35 mg/kg	6
				4 mg/kg	6
				12 mg/kg	6
NCT03754309 (KY1005-CT02 Example 2 above)	Atopic Dermatitis	Intravenous	Q4W	500 mg	30
				200 mg	29
NCT04449939 (KY1005-CT04 Example 3 above)	Healthy Volunteer	Intravenous	Single Dose	250 mg	8
		Subcutaneous		125 mg	8
				250 mg	8

*Dose denotes the loading dose. For multiple dose regimens, the follow-up dose was half the loading dose.

The provided source data were used to program one master dataset in the IntiQuan General Dataset Format [IntiQuan GDF] comprising the pooled I.V. studies (KY1005 CT01 [as described in Example 1 above] and KY1005 CT02 [as described in Example 2 above]) and the I.V. + S.C. study KY1005 CT04 [as described in Example 3 above]. The master dataset contained both KY1005 concentration PK and EASI-score PD readouts. The master dataset was employed to derive a modeling datasets for I.V. population PK model building, S.C. population PK model building, and exploratory exposure response analysis.

Based on the master dataset, the population PK analysis dataset was prepared.

The analysis dataset of I.V. and S.C. administration used for the population PK analysis consisted of a total of 1914 serum concentration samples, obtained from 113 subjects.

Table 27 provides an overview of PK sample numbers. From the total of 1914 serum PK samples, 118 were below the lower limit of quantification, only 6 of them observed after the first dose. For 95

samples either time or concentration information was missing. Additional 3 records were manually removed. The number of excluded records sum up to 216.

Table 27: Summary of available PK observations

Data	N Subjects	N samples	N BLOQ samples*	N BLOQ samples post first dose*	N missing observations	N total ignored observations	N samples included in analysis
KY1005 CT-02	59	873	61 (6.99%)	2 (0.229%)	42 (4.81%)	105 (12%)	768 (88%)
KY1005 CT-04	24	366	28 (7.65%)	4 (1.09%)	53 (14.5%)	81 (22.1%)	285 (77.9%)
KY1005 CT-01	30	675	29 (4.3%)	0 (0%)	0 (0%)	30 (4.44%)	645 (95.6%)
TOTAL	113	1914	118 (6.17%)	6 (0.313%)	95 (4.96%)	216 (11.3%)	1698 (88.7%)

Table 28: Summary of the available EASI-score observations

Data	N Subjects	N samples	N total ignored observations	N samples included in analysis
KY1005 CT-02	88	574	1 (0.174%)	573 (99.8%)
TOTAL	88	574	1 (0.174%)	573 (99.8%)

The analytical approach was based on principles established in the "Guidance for Industry Population Pharmacokinetics" [FDA 1999, FDA 2019] and "Guidance on Reporting the Results of Population Pharmacokinetic Analyses" [EMEA 2007].

The analysis was performed on the validated IntiQuan computer system [IntiQuan 2020], using a non-linear mixed effects modelling approach with a qualified installation of NONMEM (version 7.4.3 - GNU Fortran 95 compiler). The Stochastic Approximation Expectation-Maximization (SAEM) method in NONMEM was used as parameter estimation algorithm with a subsequent importance sampling (IMP) step for refinement of the objective function as suggested in [ICON 2017]. R (version 3.6.3) was used in the analysis for pre- and post-processing of data and model outputs.

Free (unbound) serum concentrations of KY1005 were assessed in blood samples taken during the study using a validated enzyme-linked immunosorbent assay (ELISA) bioanalytical method.

Model building for the population PK analysis was conducted sequentially for I.V. and S.C. administration:

1. First, a population PK model of I.V. administration was developed based on the pooled KY1005-CT01 and KY1005-CT02 I.V. data.
2. Subsequently, the I.V. population PK model was extended by also considering S.C. data from study KY1005-CT04, with a main focus on S.C. absorption parameters (absorption rate and bioavailability).

To assess the time to reach steady state, simulations were performed with a constant infusion rate. The simulation time was 52 weeks. Simulations were inspected by eye to confirm that the simulated PK concentrations had reached the plateau level (steady-state concentration). The time to reach 90% and 95% of the steady-state concentration was determined from the simulated concentration-time courses. Simulations were performed for possible combinations of the relevant covariates (bodyweight, indication, gender) using the corresponding typical population PK model parameters.

To identify a possible efficacy threshold of C_{min}, average concentration (C_{avg}), or accumulated C_{avg}, and to assess the available information in the data to support the potential future development of a PK-PD model, the individual clinical response (EASI-Score relative change from baseline) was plotted over the simulated exposure metrics.

- For each individual with EASI readout, the individual PK parameters were employed to simulate the individual PK profile and derive individual C_{min}, C_{avg}, accumulated C_{avg} values after 4, 8, 12, and 16 weeks
- Only placebo and individuals treated with 4 doses were included in the analysis. Subjects with missing doses were excluded
- The baseline EASI-Score (EASI0) was defined as the last observed EASI-Score before the start of the treatment
- The relative change of EASI was defined as (EASI-EASI0)/EASI0
- To improve the visibility of the effect, datapoints were binned and the mean and standard deviation was evaluated per bin

The final population PK model describing both I.V. and S.C. administration was characterized as follows:

- Linear two-compartmental distribution model with dosing compartment
- Bolus administration into the dosing compartment with bioavailability and lag time to represent S.C. administration
- Zero-order administration into the central compartment to represent I.V. administration
- Linear elimination
- Random effects on all model parameters (variability fixed to 5% CV for Fabs1)
- Proportional error model
- Bodyweight at baseline as a covariate on CL, Vc, and Vp1
- Indication (AD) as a covariate on CL
- Estimated correlations between random effects for Vc, Vp1 and CL

The parameter estimates for the final model are reported in Table 29. The reported shrinkage was stratified by route of administration. Terminal half-lives computed for typical healthy volunteers and atopic dermatitis stratified by bodyweight are shown in Table 30.

Table 29: Parameter estimation table of the final I.V. + S.C. population PK model

PARAMETER	VALUE	RSE	SHRINKAGE [ADMIN = SC]	SHRINKAGE [ADMIN = IV]	COMMENT
Typical parameters					
Vc	3.26	2.17%	-	-	Central volume (L)
Vp1	2.43	1.77%	-	-	Peripheral volume (L)
CL	S	3.95%	-	-	Clearance (L/day)
ka	0.222	15.2%	-	-	Absorption rate (1/day)
Fabs1	0.779	3.11%	-	-	Bioavailability (.)
Q1	0.626	11.7%	-	-	Intercompartmental clearance (L/day)
Tlag1	0.0387	16.3%	-	-	Lag-time for SC administration (days)
Inter-individual variability					
omega(Vc)	0.181	9.51%	40.5%	2.3%	LogNormal
omega(Vp1)	0.142	8.81%	54.3%	7.4%	LogNormal
omega(CL)	0.257	8.82%	43.7%	6.1%	LogNormal
omega(ka)	0.477	30.8%	-1.4%	100%	LogNormal
omega(Fabs1)	0.05 (FIX)	-	95.3%	100%	LogitNormal
omega(Q1)	0.479	25.7%	23.1%	54.8%	LogNormal
omega(Tlag1)	0.384	31.6%	4.2%	100%	LogNormal
Correlation of random effects					
corr(Vc,Vp1)	0.926	2.02%	-	-	Correlation coefficient
corr(Vc,CL)	0.492	24.5%	-	-	Correlation coefficient
corr(Vp1,CL)	0.127	132%	-	-	Correlation coefficient
Parameter-Covariate relationships					
beta_CL(WT0)	0.707	28.7%	-	-	Bodyweight at baseline in kg on CL (centered around: 75 kg)
beta_CL(IND_1)	0.26	4.61%	-	-	Indication AD on CL
beta_Vc(WT0)	0.635	24.3%	-	-	Bodyweight at baseline in kg on Vc (centered around: 75 kg)
beta_Vp1(WT0)	0.714	17.6%	-	-	Bodyweight at baseline in kg on Vp1 (centered around: 75 kg)
Residual Variability					
error_PROP1	0.154	0.804%	22.8%*	5.01%*	Proportional Error (fraction) - Concentration
Objective function	6801	-	-	-	-
AIC	6843	-	-	-	-
BIC	6957	-	-	-	-

Model: ../Models/62_Modeling_NLME_Cov_IV_SC/MODELCOV01, Significant digits: 3 (Objective function rounded to closest integer value), omega values and error model parameters reported in standard deviation.

Shrinkage was determined for separate groups of subjects stratified by ADMIN (Route of administration).

The objective function was determined using importance sampling (IMP) with settings EONLY=1 and MAPITER=0, as suggested in the NONMEM manual.

Table 30: Model-derived terminal half-life stratified by indication and bodyweight

Indication	Body weight	Terminal half-life
Healthy Volunteer	50 kg	35 days
	75 kg	34.8 days
	100 kg	34.8 days
	120 kg	34.8 days
Atopic Dermatitis	50 kg	27.2 days
	75 kg	27.1 days
	100 kg	27.2 days
	120 kg	27.2 days

Half-life determined from terminal slope. Values rounded to 3 significant digits.

Graphical exploration of the PK data

FIG. 18 and **FIG. 19** show dose-normalized PK profiles of I.V. and S.C. administration over the first 28 days stratified by study.

The dose-normalized I.V. profiles (**FIG. 18**) showed a two-phasic behavior in alignment with the assumed two-compartmental distribution model. The profiles appeared to be consistent between the different studies as indicated by the overlay of the mean dose-normalized profiles (LOESS smoothers of the three studies shown in blue in the panels per study were overlayed in different colors in the "Pooled" panel, **FIG. 18D**). The observed variability between individual PK profiles appeared higher in the patient study (KY1005 CT-02, **FIG. 18B**) than in the healthy volunteer studies (FIH, KY1005 CT-04, **FIG. 18C**).

The dose-normalized S.C. profiles (**FIG. 19**) were consistent among each other. The profiles were densely sampled during the first day and during the first week. The maximum concentration (C_{max}) was reached between 4 and 14 days. The profiles after 14 days were much flatter than the I.V. profiles.

None of the individual profiles showed an abrupt increase in clearance at any time during the first 28 days (Figure 1) or at later time points (data not shown). In conclusion, there was no indication of anti-drug antibodies (ADA) in the observed PK profiles of the different studies.

In KY1005 CT-01 (as described in Example 1 above), a nonlinearity was observed for the lowest dose groups (0.006, 0.018, and 0.05 mg/kg). Since the PK assay measured free KY1005 concentration, this nonlinearity was due to the initial binding of KY1005 to the target upon administration (TMDD). For doses of 0.15 mg/kg and above, KY1005 concentrations were high enough that this nonlinearity was not observed any more.

Simulations of exposure metrics based on the population PK model

The complete set of simulations is not shown, however simulations included simulations of the induction period with variable dose, simulations of the induction period with variable regimen and simulations of the maintenance period. Summary plots are shown in **FIGS. 20-22**. Simulated KY1005 PK profiles for selected induction scenarios stratified by body weight are shown in **FIG. 23**.

An overall summary of the simulations is shown in **FIG. 24** (Induction Period) and **FIG. 25** (Maintenance Period). For the induction period (**FIG. 24**), all simulated C_{min} values at Week 24 were collected and plotted over the dose. Different regimens (Q2W (**FIG. 24A**), Q4W (**FIG. 24B**), Q6W (**FIG. 24C**), Q8W (**FIG. 24D**)) were distributed over different panels. A similar plot was produced for the Maintenance Period (**FIG. 25**). The plot shows the percentage of time during the Maintenance Period where the concentration was above the reference C_{min} value. Different regimens (Q8W (**FIG. 25A**), Q12W (**FIG. 25B**), Q16W (**FIG. 25C**)) were distributed over different panels. The dose indicated on the x-axis refers to the loading dose. Subsequent doses were half the loading dose. In particular, all doses during the maintenance period were half of the indicated loading dose.

I.V. + S.C. population PK model

To describe S.C. administration, the I.V. population PK model was extended by a dosing compartment, bolus administration into the dosing compartment, and first order absorption from the dosing into the central compartment.

Because the PK profiles for S.C. administration provided several observed samples shortly after the time of administration, it was possible to identify a lag time of approximately one hour for the S.C. bolus administration.

Random effects were considered on all parameters. Based on the pooled KY1005 CT-01 (as described in Example 1 above), KY1005 CT-02 (as described in Example 2 above), and KY1005 CT-04 (as described in Example 3 above) data, it was possible to identify the previously fixed inter-individual variability of Q1. Also, the variability of ka and Tlag1 was identifiable. Individual estimates for Fabs1, however, were highly consistent. Given the low proportion of subjects with SC observations, the inter-individual variability of Fabs1 could not be estimated and was fixed.

The estimated random effects did not indicate new parameter-covariate relationships. Relationships established for the I.V. population PK model were revisited indicating that the impact of female gender on CL was lower than previously estimated. Therefore, besides bodyweight, indication was the only remaining covariate considered in the final population PK model. The higher clearance in patients could possibly be explained by the generally higher target expression in patients, and specifically in skin where KY1005 would distribute to.

Correlations between random effects based on the pooled I.V. + S.C. data were confirmed as established. Further correlations between random effects involving the S.C. population PK model parameters were not considered due to the low proportion of subjects with S.C. observations.

VPCs of I.V. of S.C. administration confirmed the adequacy of the final population PK model. The previously underpredicted observations 168 days after the last dose were better captured by the final population PK model. Because the observed median was at the upper limit of the 95% uncertainty band of the predicted median, the possibility of a potential underprediction of late time points will be further investigated on the basis of new KY1005 CT-02 (as described in Example 2 above) long-term data. VPCs stratified by study did not show indications of inconsistency between the pooled studies. Consequently, the final population PK model was found to be qualified for the conduct of simulations.

Simulations

Simulations were performed for I.V. reference dosing schemes in healthy volunteers and S.C. dosing schemes in patients. Simulations for patients were distinguished by induction period (0 to 24 weeks) and maintenance period (24 to 52 weeks). The main exposure metric of interest for the induction period was the C_{min} after 24 weeks in comparison to the C_{min} of the reference dose. For the maintenance period, the C_{min} after 52 weeks and the time above C_{min} of the reference dose during the maintenance period were the key metrics.

Simulations of the induction period indicated that with a fixed Q4W regimen, the threshold to reach $C_{min} > C_{min,ref}$ was around 50 mg (loading dose, half the loading dose for subsequent doses). This threshold dose would be around 125 mg (loading dose, half the loading dose for subsequent doses) for Q6W and 200 mg for Q8W.

Simulations of the maintenance period indicated that Q8W and Q12W were generally feasible regimens allowing $C_{min} > C_{min,ref}$ after 52 weeks for doses not higher than 500 mg (loading dose, half the loading dose during maintenance period). The Q8W regimen allowed to maintain the C_{min} above the reference C_{min} across all body weights (50 kg to 120 kg) for loading doses higher than 350 mg. For the Q12W regimen, 500 mg loading dose were sufficient to stay above the reference C_{min} for a bodyweight of 50, 75, and 100 kg but not for 120 kg. For the Q16W regimen, the concentration dropped below the reference C_{min} at some time between 24 and 52 weeks for almost all combinations of dose and bodyweight. In particular, for heavy patients (100 and 120 kg) a 100% fraction of time above the reference C_{min} could not be maintained for any of the doses up to 500 mg (loading dose) in the Q16W regimen.

Exploratory exposure response analysis

The exposure response data was highly variable and did not allow to precisely constrain the Cmin of the half-maximum efficacy (EC_{50}). The data suggested that the EC_{50} would be below the C_{min} = 10 to 20 μg/mL region. Thus, the choice of the simulated reference dose of 0.45 mg/mL (loading

dose, half the loading dose for subsequent doses) Q4W I.V. leading to C_{min} between 3.3 and 4.2 μg/mL was consistent with the exposure response data.

Conclusions

A population pharmacokinetic model was developed to support the dose selection in the upcoming Phase IIb study by simulations.

The final population pharmacokinetic model adequately describing the dose-concentration relationship was characterized as follows:

- Two-compartmental distribution model with dosing compartment.
- Bolus administration into the dosing compartment with bioavailability and lag time to represent subcutaneous administration.
- Zero-order administration into the central compartment to represent intravenous administration.
- Linear elimination.
- Random effects on all model parameters (inter-individual variability fixed to 5% coefficient of variance for subcutaneous bioavailability).
- Proportional residual error model.
- Bodyweight at baseline as a covariate on clearance, central volume, and peripheral volume.
- Indication (atopic dermatitis) as a covariate on clearance.
- Estimated correlations between random effects for central volume, peripheral volume, and clearance.

The subcutaneous bioavailability was estimated to be 0.779. The 95% confidence interval ranged from 0.731 to 0.827.

The terminal half-life was estimated to be around 35 days for healthy volunteers and around 27 days for atopic dermatitis patients.

Simulations of a virtual patient population treated subcutaneously identified feasible dose and regimen windows exceeding a targeted trough concentration during a 24 week induction period. A prolonged regimen of up to Q12W during maintenance period seemed feasible.

The choice of the simulated reference dose of 0.45 mg/mL (loading dose, half the loading dose for subsequent doses) Q4W intravenously leading to trough concentrations between 3.3 and 4.2 μg/mL was consistent with the analysis of the exposure response data.

Example 5: A Phase IIb, Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter Dose Ranging Study of a Subcutaneous Anti-OX40L Monoclonal Antibody (KY1005) in Moderate to Severe Atopic Dermatitis (KY1005-CT05)

Study Purpose

The aim of this study is to characterize the efficacy (including dose/exposure response) and safety of KY1005 across a range of doses/exposures for a maximum duration of 52 weeks in adult patients with moderate-to-severe AD who have had an inadequate response to topical therapies or where topical therapies are not advised. In addition, the durability of response and Pharmacokinetic (PK) characterization following withdrawal from KY1005 from Week 24 will be characterized.

Primary Objective

To characterize the efficacy (including dose/exposure-response) across a range of KY1005 exposures compared to placebo on the signs of AD using the Eczema Area and Severity Index (EASI) in those patients who have who have a documented history, within 6 months prior to baseline, of either inadequate response to topical treatments or inadvisability of topical treatments.

Secondary Objectives

- Asses the safety and tolerability of KY1005.
- The pharmacokinetic profile across a range of KY1005 doses/exposures.
- The response across a range of KY1005 exposures on additional physician assessments of AD activity/severity (EASI-50, EASI-75, EASI-90, EASI-100, Investigator Global Assessment [IGA], SCORAD Index and BSA).
- The response across a range of KY1005 dose/exposures on patient reported AD activity/severity (Atopic dermatitis Control Tool [ADCT], POEM, DLQI, Hospital Anxiety and Depression Scale [HADS], and NRS for pruritus).
- The pharmacodynamic response to KY1005 including but not limited to: the immunogenicity of KY1005, including the anti-KY1005 antibody response.
- The explore the continued clinical response in those patients who achieve ≥ EASI-75 or who attain IGA0/1 at Day 169.

Primary Endpoint

- Percentage change in EASI from Baseline to Day 113.

Secondary Endpoints

- Incidence of treatment-emergent adverse events.
- Serum KY1005 concentration assessed throughout the study.
- Percentage change from Baseline in EASI at Day 169.
- Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI-75) at Days 113 and 169.
- Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥ 2 points at Days 113 and 169.
- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥ 4 with a Baseline pruritus NRS of ≥ 4 from Baseline to Days 113 and 169.
- Absolute change from Baseline in EASI at Days 15, 29, 57, 85, 113, 141 and 169.
- Percentage change from Baseline in EASI at Days 15, 29, 57, 85 and 141.
- Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI-50) at Days 15, 29, 57, 85, 113, 141 and 169.
- Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI-75) at Days 15, 29, 57, 85, and 141.
- Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI-90) at Days 15, 29, 57, 85, 113, 141 and 169.
- Percentage of patients with at least a 100% reduction from Baseline in EASI (EASI-100) at Days 15, 29, 57, 85, 113, 141 and 169.
- Change in IGA from Baseline to Day 169 and over time.
- Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥ 2 points at Days 15, 29, 57, 85, and 141.
- Absolute and Percentage in SCORAD Index from Baseline to Day 169 and over time.
- Absolute and Percentage change in affected BSA from Baseline to Day 169 and over time.
- Absolute and Percentage change in POEM, DLQI, ADCT, and HADS from Baseline to Day 169 and over time.
- Absolute and Percentage change in weekly average of pruritus NRS from Baseline to Day 169 and over time.
- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥ 3 with a Baseline pruritus NRS of ≥ 3 from Baseline to Days 113 and 169.
- The immunogenicity of KY1005, including the anti-KY1005 antibody response.
- Continued assessment of the efficacy endpoints from Day 169 and over time.
- Time to loss of EASI-75, IGA0/2, and EASI-50 in participants randomized to withdrawal post-Week 24.
- Continued assessment of patient reported AD activity/severity endpoints from Day 169 and over time.

Study Design

This is a Phase IIb, randomized, double-blind, placebo-controlled, parallel group, multicenter dose ranging study to characterize the efficacy and safety of S.C. administered KY1005 in adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to baseline, of an inadequate response to, or inadvisability of, topical treatments.

After providing informed consent, patients will be assessed for study eligibility at the Screening Visit. Patients will undergo Screening within 28 days prior to randomization. During the Screening period, treatments for AD will be washed out for at least 7 days prior to baseline (except bland moisturizers). Patients will be required to apply bland moisturizers (emollients) with no additives (e.g., urea) at least twice daily for a minimum of 7 consecutive days before baseline and continue throughout the study.

Up to 350 patients (approximately 70 patients per treatment arm) will be enrolled. Patients who continue to meet the eligibility criteria at Baseline will be randomized to 1 of 5 treatment groups (4 different KY1005 regimens or Placebo) in an equal (1:1:1:1:1) ratio.

From baseline up to Day 169 (Week 24) IMP will be administered at the following dose and intervals:

- 500 mg loading at baseline (2 x 2 mL injections of 250 mg) followed 4 weeks later with 250 mg Q4W as 1 x 2 mL injection;

OR

- 250 mg (as 1 x 2 mL injection) plus 1 x 2 mL Placebo at Baseline followed 4 weeks later with 250 mg Q4W as 1 x 2 mL injection;

OR

- 125 mg (as 1 x 2 mL injection) plus 1 x 2 mL Placebo at Baseline followed 4 weeks later with 125 mg Q4W as 1 x 2 mL injection;

OR

- 62.5 mg (as 1 x 2 mL injection) plus 1 x 2 mL placebo at Baseline followed 4 weeks later with 62.5 mg Q4W as 1 x 2 mL injection;

OR

- Placebo given as 2 x 2 mL injections at Baseline followed 4 weeks later with 1 x 2 mL Placebo (0 mg).

At baseline, those patients not receiving a KY1005 loading dose will receive both KY1005 and Placebo to maintain the study blind.

The primary analysis will occur when all patients have completed Day 113 (or earlier in the event of termination).

To enable Placebo patients and those patients randomized to the KY1005 62.5 mg Q4W and 125 mg Q4W treatment arms to receive KY1005 at a dose expected to elicit a meaningful clinical response (based on prior clinical evidence), patients who do not achieve greater than or equal to EASI-75 or IGA0/1 at Week 24 will be invited to enroll in the long-term extension (LTE) study where they will receive 250 mg Q4W KY1005.

In those patients who achieve greater than or equal to EASI-75 or who attain IGA0/1 at Week 24, a randomization will occur pre-dose at Day 169 (Week 24). This will occur irrespective of whichever dose group the patient was randomized to at baseline including placebo. Patients will be randomized in a 3:1 manner to be withdrawn from therapy or to continue their pre-Week 24 dose/interval. To maintain the blind, those patients randomized to the Withdrawal arm will receive Placebo Q4W. Those patients who are randomized to the Withdrawal arm who lose their clinical response will be offered the opportunity to be retreated with KY1005 in the LTE study. Loss of clinical response is defined as the first instance of ≤ EASI-50 at any point in the study. If loss of clinical response from Week 28 occurs, Investigators will be able to choose to discontinue the patient from KY1005-CT05 or to progress to the LTE study. If loss of response from Week 28 occurs between visits and retreatment with KY1005 is considered appropriate, patients will be permitted to move to the LTE study (subject to meeting the inclusion/exclusion criteria for the LTE) at that time. Waiting until the next scheduled visit will not be required.

At Day 365 (Week 52), patients who have completed the post-Week 24 period will have the opportunity to be considered for enrolment into the LTE protocol. All patients who do not meet the inclusion criteria for the LTE, or where the patient declines to continue participation in the study or subsequent the LTE study, will have an additional 84 days safety follow-up up to Day 449 (Week 64) and then be discharged from the study. The last dose will be given no later than Day 337 and as such safety follow-up will be 112 days following last dose of KY1005.

Skin punch biopsies (5 mm) will be taken in up to approximately one third (30%) of patients who will be enrolled into a skin biopsy sub-study. This will be done at selected sites. Lesional and non-lesional samples will be collected at Baseline with lesional samples requested at Day 113.

The overall study design is presented in **FIG. 26**.

Patients and Inclusion Criteria

Up to 350 patients (approximately 70 patients per treatment arm at Baseline) will be randomized.

Patients must fulfill all the following inclusion criteria for entry into the study:

1. Adults (18 to < 75 years of age) with AD as defined by the American Academy of Dermatology Consensus Criteria [Eichenfield *et al.*, 2014] for 1 year or longer at Baseline.
2. EASI of 12 or higher at the Screening Visit and 16 or higher at Baseline.
3. IGA of 3 or 4 at Baseline.
4. AD involvement of 10% or more of body surface area (BSA) at Baseline.
5. Baseline worst/maximum pruritus NRS of ≥ 4. The baseline weekly average of daily worst/maximum pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline visit. A minimum of 4 daily scores out of the 7 will be required.
6. Documented history, within 6 months prior to Baseline, of either inadequate response or inadvisability of topical treatments.
7. Must have applied a stable dose of topical bland emollient (simple moisturizer, no additives [e.g., urea]) at least twice daily for a minimum of 7 consecutive days before baseline.
8. Able to complete patient questionnaires, including collection of NRS (pruritus) on each of the 7 days prior to baseline. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening.
9. For patients at sites selected for skin biopsy collection: (until up to approximately one third (30%) of patients have enrolled to the skin biopsy sub-study), able and willing to provide skin biopsies at required timepoints.

Exclusion Criteria

Patients fulfilling any of the following exclusion criteria will be excluded from the study:

1. Treatment with any of the following prior to first IMP administration (Baseline):
   - Systemic corticosteroids, and calcineurin inhibitors (tacrolimus and cyclosporin) within 4 weeks;
   - Leukotriene inhibitors within 4 weeks;
   - Use of mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin, Kineret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion within 4 weeks prior to Baseline;
   - Use of infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, IFN-γ, janus kinase (JAK) inhibitors, dupilumab, and any other biologic or targeted-synthetic disease modifier drug not mentioned in this exclusion criterion or in the exclusion criterion above, as well as plasmapheresis within 12 weeks prior to baseline;

- Use of anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics within 6 months prior to baseline (or shorter if there is documented B cell reconstitution for anti-CD20 drugs);
- Topical corticosteroids, tacrolimus or pimecrolimus, or topical phosphodiesterase-4 (PDE4) inhibitor within 7 days;
- Prescription or non-prescription moisturisers with additives (e.g., urea, filaggrin) within 2 weeks;
- Dupilumab (aIL-4Rα) within 3 months;
- Any prior use of any anti-OX40, anti-OX40L mAb;
- Investigational therapy for the treatment of AD or other conditions within 5 half-lives or the limit of PD effects or 3 months where the t1/2 is not known.

2. Weight < 40 kg or > 150 kg at baseline.

Other inclusion/exclusion criteria as standard for this type of trial will be used.

Investigational Medicinal Product

The IMPs are KY1005 (SAR445229), or matching Placebo.

KY1005 drug product is formulated as a liquid at 125 mg/mL.

KY1005 125 mg/mL drug product is aseptically filled into 2 mL Type 1 clear glass vials with a nominal fill volume of 1 mL, sealed with FluoroTec coated stoppers and crimped with overcaps to ensure container closure integrity.

The matching Placebo is used to dilute KY1005 to the correct dose concentration in a fixed volume to maintain blinding.

Treatment Regimen

Patients may receive study treatment every 4 weeks from Day 1 to Day 337 (Week 48) according to the scheme in **FIG. 26**.

Table 31: Treatment Regimens

Arm	Day 1		Day 29 to Day 169			Day 169 to Day 365 in patients who achieve ≥ EASI-75 or who attain IGA0/1at Day 169		
	IMP	Dose (mg)	Frequency	Dose (mg)	Frequency	IMP	Dose (mg)	Frequency
1	KY1005	500 mg (2 x 250 mg)	Q4W	250 mg	Q4W	KY1005	250 mg	Q4W *or*
						PBO	0	Q4W
2	KY1005		Q4W	250 mg	Q4W	KY1005	250 mg	Q4W *or*

		250 mg plus				PBO	0	Q4W
3	KY1005	125 mg plus PBO loading	Q4W	125 mg	Q4W	KY1005	125 mg	Q4W *or*
						PBO	0	Q4W
4	KY1005	62.5 mg plus PBO loading	Q4W	62.5 mg	Q4W	KY1005	62.5 mg	Q4W*or*
						PB0	0	Q4W
5	Placebo	NA plus PBO loading	Q4W	NA	Q4W	PBO	0	Q4W *or*
						PBO	0	Q4W

IMP=investigational medicinal product; PBO= Placebo; NA=not applicable; Q4W=every 4 weeks.

All study treatment regimens are presented in Table 31. Randomization will occur pre-injection on Day 1, with re-randomization pre-injection on Day 169 should the patient achieved an ≥ EASI75 or attain IGA0/1.

From Day 169 (Week 24) to Day 365 (Week 52) in patients who achieve 2 EASI-75 or who attain IGA0/1 at Week 24 will be randomized 3:1 to either Withdrawal or will continue to receive their pre-Week 24 dosing.

Patients randomized to Withdrawal will receive Placebo Q4W. Those patients not randomized to Withdrawal will continue to receive their pre-Week 24 dose/interval.

Re-randomization from Day 169 will not be uncoded to the team, study sites or patients until after the final Data Base Lock. Those patients who do not achieve 2 EASI-75 or IGA0/1 at Week 24 will have the possibility to enroll into the LTE where they will receive KY1005 250 mg Q4W.

All doses of KY1005 and Placebo will be administered in a 2.0 mL volume. At Baseline, 2 x 2 mL injections will be given to maintain the integrity of the blind.

Administration of IMP

At the Baseline visit only, 2 S.C. injections will be administered. At all remaining visits, 1 injection will be administered. KY1005 or matching Placebo will be administered as a S.C. injection to the abdomen. If IMP administration to the abdomen is not possible due to the extent of skin involvement, the outer thigh may be selected.

Treatment Duration

All patients treated with KY1005 or matching Placebo will be randomized and begin study treatment on Day 1. Patients will initially receive S.C. injections of IMP (Days, 1, 29, 57, 85 and Day 113) ahead of the primary efficacy analysis at Day 113 (Week 16). Treatment will then continue to Day 169 (Week 24). Those patients in the 500 mg loading with 250 mg Q4W treatment arm will receive 2 x 2 mL 250 mg S.C. injections on Day 1 and commence 250 mg Q4W on Day 29. Those

in the remaining treatment arms will receive their assigned KY1005 dose as a 2 mL injection also receive a 2 mL injection of Placebo on Day 1 to maintain the blind and commence their assigned KY1005 or Placebo Q4W dose on Day 29.

Those patients who achieve 2 EASI-75 or who attain IGA0/1 at Week 24 will be re-randomized pre-injection at Day 169 (Week 24) to either the Withdrawal arm (and receive Placebo Q4W) or remain on their pre-Week 24 dose.

The duration of treatment will therefore be up to Day 365 (Week 52), with last dose administered on Day 337 for those patients who achieve 2 EASI-75 or who attain IGA0/1 at Week 24, unless enrolled into the LTE study.

Those patients who do not achieve 2 EASI-75 or IGA0/1 at Week 24 will have the possibility to enter the LTE at Day 169.

Background Therapy

Patients are required to apply a stable dose of a topical bland emollient (simple moisturizer) at least twice daily for a minimum of 7 consecutive days before the baseline visit and to continue with the same emollient at the same dose twice daily throughout their participation in the study.

To permit an adequate assessment of skin dryness, moisturizers should not be applied on area(s) of non-lesional skin, designated as such for assessment purposes, for at least 8 hours before each clinic visit.

Patients are permitted to use any simple bland prescription, over-the-counter or general purchase moisturizer providing it contains no additives, such as corticosteroids or urea (even at low concentrations). Prescription and non-prescription moisturizers with additives (e.g., urea, filaggrin) are not permitted within 2 weeks prior to first IMP administration (Baseline) or during the study.

Efficacy Assessments

The efficacy of KY1005 in the treatment of AD will be assessed using change in EASI, IGA, SCORAD Index and affected BSA. Investigator performed assessments should be carried out by the same assessor on each occasion for an individual patient. Patient reported outcomes will be assessed using the POEM, DLQI, HADS, ADCT and the NRS for pruritus. Patients will be required to use an internet-enabled device (e.g., computer, mobile phone or tablet device) to complete an electronic diary to record the PROs in local languages where validated. Patients should bring their eDiary to visits and review with coordinators. Patients will be encouraged to continue completing diary information until their last visit.

Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of study drug. The PRO assessments performed with include EASI, v-IGA, SCORAD Index, BSA Involvement of Atopic Dermatitis, POEM, DLQI, and NRS for Pruritus (See Example 2 for a description of these PRO assessments.) Additionally, the ADCT and HADS will be assessed and are described below.

Atopic Dermatitis Control Tool (ADCT)

The ADCT is a validated 6-item instrument with a 7-day recall period to measure AD disease control. The following domains are assessed - overall severity of symptoms, frequency of intense episodes of itching, severity of bother of itching, frequency of sleep impact, severity of daily activities impact, severity of mood or emotions impact. Each item is scored from 0 (none) to 4 (extreme). A total score of 7 or more points (derived by adding item scores) was identified during validation as an optimum threshold to identify patients whose AD is "not in control".

Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item patient reported outcome measure used to assess states of anxiety and depression over the past week.

Pharmacokinetic Procedures

Blood samples will be withdrawn periodically for KY1005 assay. Pharmacokinetic and ADA samples will be collected from all patients including those receiving Placebo.

Serum concentrations of KY1005 will be assessed from blood samples taken during the study using validated enzyme-linked immunosorbent assay (ELISA) bioanalytical methods. Assay methodologies and procedures will be described in analytical plans to be finalized before the start of sample analysis.

The following PK values will be derived for each patient receiving KY1005 and all KY1005 regimens:

C_{max} following the first, or any doses where sampling permits. Peak concentrations following any doses where sampling permits.

t_{max} following the first, or any doses where sampling permits.

C_{min} following the first, second, third, fourth and any doses where sampling permits.

Anti-drug Antibody Procedures

Blood samples will be withdrawn periodically for anti-KY1005 antibody assays. Serum titers of anti-KY1005 antibodies will be assessed in blood samples taken during the study using a validated bioanalytical method. Characterization of positive ADA samples, e.g., KY1005 neutralizing capacity, may be performed if required.

Example 6: Treatment with KY1005 - a novel non-depleting anti-OX40Ligand (OX40L) mAb - reduces IL-13 serum levels in a Phase 2a randomised placebo-controlled trial on patients with moderate to severe Atopic Dermatitis.

Methods

Serum was collected during the trial (Ph2a monotherapy, NCT03754309, Kymab-funded, 16-week, double-blind, RCT). 89 moderate-to-severe AD patients were randomised 1:1:1 to i.v. KY1005 low dose (KY1005-Lo, 200 mg loading/100 mg maintenance Q4W), high dose (KY1005-Hi, 500 mg /250 mg Q4W) or placebo (PBO). Disease severity measurement included EASI. Serum IL-13 levels were determined by single molecule immunoassay (Simoa).

Results

Of 88 subjects who received KY1005, 59 were evaluable at W16. KY1005 was well tolerated with unremarkable safety profile. Mean % change in EASI from baseline (BL) at W16 was -80.1% for KY1005-Lo and -69.9% for KY1005-Hi vs -49.4% for PBO ($p=0.009$ and 0.072 respectively). No BL difference in IL13 was found between groups. IL-13 levels correlated with disease severity at BL ($r=0.4784$, $p<0.0001$). A significant reduction in IL13 levels was observed at W16 in KY1005-treated patients (Lo $p<0.0001$; Hi $p=0.0003$) but not PBO ($p=0.1558$).

Example 7: KY1005-CT02: Analysis of Serum Proteins

Study Summary

IL-22, IL-13, IL-31 and IL-17A were identified to be significantly associated with disease severity as measured using EASI scores. When treatment-induced changes in serum protein levels upon KY1005 and Placebo treatment at Day 113 were assessed, IL-22, IL-13, IL-31 and IL-17A were found to be significantly changed upon KY1005 treatment. IL-22, IL-13, IL-31 and IL-17A were found to be affected by KY1005, but not Placebo treatment, suggesting that these proteins are specifically affected by KY1005.

Study objective

Olink technology provides the means to assess serum levels of many proteins in parallel using small samples volumes. IL-17A was quantified using Olink. In addition, serum levels of IL-13, IL-22

and IL-31 were analysed using the highly-sensitive Simoa technology. The aim of this study was to identify circulating biomarkers which are affected by KY1005 treatment.

Patient cohort

Serum samples were collected from all patients enrolled in KY1005-CT02. Serum was collected from all patients at baseline (day 1 of the trial), day 29 and day 113. In the study extension phase, further serum samples were collected at day 169 and day 253 from responders only (= patient who reached a vIGA score of 0 or 1 at the primary endpoint on day 113)

For SIMOA analysis, 264 samples in total. Samples collected from 10 patients were only used for analyses independent of clinical scores (EASI, SCORAD, vIGA). 5 samples did not contain enough volume for all assays. All statistical tests were performed on log-transformed data, as IL-13 and IL-22 levels are log-normally distributed.

Serum collection

At clinical sites, blood was collected by venipuncture into 5mL SST serum(Gel)-Vacutainer tubes (BD). Immediately after blood collection, the tube was very gently agitated by turning the tube upside-down 8-10 times to ensure dissolution of the anticoagulant. To allow for blood clotting, the tube was left at ambient temperature in an upright position for approximately 30 minutes. The serum(Gel)-Vacutainer was then centrifuged for 10 minutes at 2500 g, ambient temperature in a swing bucket centrifuge if available. At least 300µL of the supernatant serum were then carefully transferred into each of four 2 mL CryoPure tubes with yellow screw caps using a fresh pipette. Contamination with erythrocytes was strictly avoided. If contamination occurred, the specimen had to be centrifuged again. All aliquots were stored upright in a -80°C freezer (ensuring a temperature of at least -70°C or below). Visit specific data was recorded in the storage list for frozen serum specimens, before dry ice shipments to the central laboratory LKF were organised. Samples were stored at LKF and shipped to Olink and Myriad RBM (Simoa) for analysis.

Olink assay

Serum samples were shipped to Olink on dry ice and stored at -80°C until tested. Samples were analysed in three batches. Upon thawing, 40 µL of each sample were aliquoted into 96-well plates in a randomised fashion. 1µL per sample and per panel were then used to quantify the serum levels of proteins using Olink panels.

The Olink reagents are based on Proximity Extension Assay technology, where proteins can be detected by antigen-specific oligonucleotide-labelled antibody probe pairs. A PCR reporter sequence is formed by a proximity-dependent DNA polymerization event. This is then amplified, and subsequently detected and quantified using real-time PCR using the Fluidigm® BioMarkTM I1D System. The assay is performed in a homogeneous 96-well format without any need for washing steps, using the 96x96 Dynamic Array™ IFC for multiplexing and an IFC loader to load the 96x96

Dynamic Array IFC. Internal controls are added to each sample and include two Immunoassay controls, one Extension control, one Detection control and one external inter-plate control used to monitor the extension and readout steps and for data normalisation across samples and different runs.

Analysis results are presented as Normalised Protein eXpression (NPX) units on a log2 scale, which are generated from the extension reaction read-out after normalisation based on internal controls and allow for relative (not absolute) quantitation of serum protein levels.

PANEL ASSAY	UNIPROT ID	OLINKID
Olink INFLAMMATION(v.3022) IL-17A	Q16552	OID00485

Simoa assay

All serum samples were stored at temperatures below -72°C until tested. Samples were thawed at room temperature, vortexed, spun at 3700 x g for 5 minutes for clarification and transferred to a master 96-well plate and diluted to the final required dilution. The assay was processed using Quanterix's fully automated immunoassay platform:

Simoa HD-1/HD-X Analyzer and single molecule array (Simoa) technology. All incubations took place at ambient temperature inside the Simoa HD-1/HD-X analyzer. Capture antibody conjugated paramagnetic beads were incubated with standards, samples, controls, and biotinylated detection antibodies. The beads were then washed and incubated with streptavidin-ß-galactosidase (SßG). After the final wash, the beads were loaded into the Simoa Disc with SßG, resorufin ß-galactopyranoside. The fluorescence signals were compared to the standard curve and the quantity of target analyte was determined for each sample. The data was interpreted using proprietary software developed by Myriad RBM. For each assay, both calibrators and controls were included on each sample plate. Eight-point calibrators were used to form a standard curve in the first and last column of each plate and controls at 3 concentration levels were run in duplicate. QC for the standard curve, controls, and samples was performed to ensure proper assay performance.

The QHSP-IL-13 SimoaTM ultra-high sensitivity assay was developed by Myriad RBM (MRBM) using Quanterix's fully automated immune assay platform and performed using up to 150 µL of serum following the steps described above. The QHSP-IL-22 Simoa™ ultra-high sensitivity assay was developed by Myriad RBM (MRBM) using Quanterix's fully automated immunoassay platform and performed using up to 100 µL of serum following the steps described above.

The QHSP-IL-31 Simoa™ ultra-high sensitivity assay was developed by Myriad RBM (MRBM) using Quanterix's fully automated immunoassay platform and performed using up to 100 µL of serum following the steps described above (Kit lot number: K15859-QHSP-IL-31). IL-31 levels were quantified in left-over serum samples, only when corresponding baseline samples from the same patient were still available (n=230, with 9 samples excluded due to missing baseline samples).

Table 32: Simoa assay specifications

Assay	N	Unit	Dilution	LDD	LLOQ	ULOQ	Dynamic Range
IL-13	260	pg/mL	1:2	0.10	0.099	500	0.099-500
IL-22	264	pg/mL	1:4	0.024	0.047	120	0.024-120
IL-31	232	pg/mL	1:4	0.033	0.024	400	0.024-400

Data analysis

Assay results were obtained from Olink. Simoa data was obtained from Myriad RBM in the form of Excel tables. Patient response information was extracted from the clinical "adrs.xpt" Adam SAS dataset.

Analysis was conducted using the statistical computer language R (version 4.0.2).

Processing and batch normalisation of the Olink data was performed with the OlinkAnalyze R package written by Olink Proteomics. The three spreadsheets of Olink data were loaded into R using the "read_NPX" function. The three resulting data objects were combined, and batch corrected using the "olink_normalization" function. Batch correction used the bridging sample and was performed in a two-step process. Both batch 2 and 3 were separately normalised to batch 1, altering the values of batch 2 and 3 samples. All three batches were then combined into a single dataset. After the initial batch correction, a residual batch effect was observed. An additional batch correction was performed using the limma function "removeBatchEffect" to remove this effect. Log2-transformed Simoa data were analysed alongside Olink data.

Linear models were performed for all time-points up to Day 113 using the base-R function 'lm'. Uniform Manifold Approximation and Projection (UMAP) dimensionality reduction plots were performed with the 'umap' package. All plots were generated using "The Grammar of Graphics" inspired 'ggplot2' data visualisation package.

Results

Numerically greater reductions in serum levels of total IgE, Th2-associated cytokines IL-13 and IL-31 and the Th22-associated cytokine, IL-22 on week 16 compared to baseline were observed in the amlitelimab high and low dose groups compared to the placebo group. In the study extension, treatment-dependent reductions of total IgE, IL-13 and IL-22 up to week 16 were also largely maintained up to week 36 in patients who maintained their vIGA0/1 status 24 weeks after the last amlitelimab dose.

Serum protein levels associated with clinical disease severity

(Table 33): Significantly different serum protein changes between KY1005 and Placebo

		DAY 29		DAY 113	
ProteinID	Protein	Estimate	Unadj.p	Estimate	Unadj.p
Simoa_IL13	IL13	-0.50261	0.025623	-0.66645	0.103372
Simoa_IL31	IL31	-0.38903	0.220672	-1.46837	0.018847

Differences in the changes in serum protein levels between KY1005-treated and Placebo patients at days 29 and 113 were assessed. Proteins with an unadjusted p-value <0.05 seen in at least one of the two timepoints are displayed in Table 33. Proteins are ordered by the magnitude of difference in protein changes (Estimate) between the Placebo and KY1005 treatment groups at day 29. Proteins decreased in KY1005 compared to Placebo are shown.

Figure 31A-31B: Proteins associated with disease severity.

IL-22 and IL-13 protein levels were found to be significantly associated (FDR p-value < 0.05) with EASI scores at baseline (first column). This association was also maintained at day 29 and day 113. The coefficient of determination R2 and p-values were calculated using linear models. Each dot represents a patient sample, the blue line represents the linear regression line, the 95% confidence interval is shown in grey. Linear modelling was performed between EASI scores and serum protein levels (EASI NPX). Analysis of baseline samples revealed a significant association (FDR p-value <0.05) between baseline EASI scores and serum levels of interleukin (IL)-22 and IL-13 (Figures 31A and 31B; Table 34).

When the sample size was increased by including all samples up to Day 113 in the analysis, IL-13, IL-22 and IL- 17A were found to be significantly (FDR <0.05) associated with AD disease severity in our cohort (Table 35). Top hits of this second analysis again included IL-22 and IL-13, which were positively correlated with EASI severity scores at all timepoints (Figure 31A and 31B).

Table 34: IL-13 and IL-22 are associated with disease severity at Baseline

ProteinID	Protein	Estimate	Unadj P	FDR
Simoa_IL22	IL22	3.3603	1.10E-06	0.000289
Simoa_IL13	IL13	4.092481	0.000155	0.020401

Linear modelling (EASI ~ NPX) was performed between baseline EASI scores (EASI) and serum protein levels (NPX). Proteins with an FDR p-value <0.05 are shown.

Table 35: IL-13, IL-22 and IL-17A are associated with disease severity at Baseline, Day 29 and Day 113

ProteinID	Protein	Estimate	Unadj P	FDR
Simoa_IL22	IL22	5.930553	7.17E-13	1.30E-10
Simoa_IL13	IL13	7.79846	9.88E-13	1.30E-10
OID00485	IL-17A	9.815526	0.000145	0.001529

Linear modelling (EASI ~ NPX + SUBJID) was performed between serum protein levels at Baseline, Day 29 and Day 113 (NPX) and EASI scores at these timepoints (EASI). Proteins with an FDR p-value <0.05 are shown.

KY1005-induced changes in serum protein levels

To further investigate potential treatment effects of KY1005, temporal changes in protein levels at Day 113 from baseline in KY1005-treated patients were analysed. Based on this analysis, it was noted that proteins IL-13, IL-22, IL-17A and IL-31 were significantly changed at D113 upon KY1005 treatment (FDR p-value <0.05; Table 36; **FIG. 32A-C** and **FIG.42**).

Table 36: IL-13, IL-22, IL-17A and IL-31 are reduced upon KY1005 and Placebo treatment

ProteinID	Protein	Estimate	KY1005 Unadj P	FDR	Estimate	Placebo Unadj P	FDR
Simoa_IL13	IL13	-1.37953	5.70E-10	7.52E-08	-0.71307	0.061703	0.191642
Simoa_IL22	IL22	-1.81296	3.82E-10	7.52E-08	-0.69007	0.191019	0.327462
OID00485	IL-17A	-0.37636	0.000405	0.00668	-0.236	0.223961	0.353614
Simoa_IL31	IL31	-1.78224	6.32E-07	2.39E-05	-0.31386	0.541913	0.656261

Statistical analysis of changes in KY1005-treated and Placebo patients at days 29 and 113 compared to baseline were performed. The proteins had changed at Day 113 compared to baseline with an unadj. p-value <0.05 in KY1005 and Placebo patients.

IgE changes upon KY1005 treatment

As part of KY1005-CT02 (NCT03754309), serum levels of immunoglobulins class E (IgEs) were quantified. Serum samples were assayed on a COBAS Modular Analytics E170 using a Elecsys IgE II kit (catalogue number 04827031-190) following the manufacturer's instructions.

IgE levels were homogeneously distributed among the treatment groups, without any significant difference among groups. The plot also confirmed that, as reported in literature, moderate to severe AD patients show higher than normal IgE levels, with ~88% of the patients with IgE levels above 100 IU/mL in our cohort. A weak but significant correlation between IgE levels and EASI score was observed.

IgE levels were plotted at baseline, day 29 and day 113 (primary endpoint) grouped by treatment, in order to compare the two KY1005 doses and placebo. Both KY1005 doses induced a significant

decrease in circulating IgE levels at day 113, and for the KY1005 low group, a significant decrease in IgE was already apparent at day 29.

Finally, the persistence of the KY1005-dependent reduction in IgE levels in the follow-up period was assessed (time-points: day 29, 113, 169 and 253) and the raw IgE values for all the available time-points (baseline, day 29, 113, 169 and 253 or baseline, week 4, week 16, week 24 and week 36) were plotted per every treatment arm. As shown in **FIG. 41 (A)**, the patients treated with KY1005 showed a persisting reduction in IgE levels achieved during the active period of the trial, and this was evident both when plotting the fold-changes from baseline and the raw IgE values.

In addition, KY1005-treated patients that were considered responders (vIGA 0-1) at Day113 demonstrated a significant reduction in IgE levels (vs baseline) by day 113 which continued to decrease up to day 253. Non-responders also demonstrated a decrease in IgE levels in response to KY1005 at day 113 (albeit less significant than responders). The decrease in IgE levels did not significantly correlate with improved clinical score in the cohort.

Effect of Amlitelimab on serum biomarkers (total IgE, IL-13, IL-22 and IL-31)

Fold change from baseline in serum (A) IgE, (B) IL-13, (C) IL-22 and (D) IL-31 over time by treatment regimen is shown in **FIG. 41**. Up to week 16, all patients with biomarker data at baseline and week 16 or at least two alternative on-treatment timepoints were included. For the study extension, only patients who achieved vIGA0/1 at week 16 (w16 responders) were included. Post-hoc linear mixed-effects model with Dunnett's multiple comparison test for log10-transformed fold change from baseline by treatment regimen (ns not significant, * $p<0.05$, ** p,0.01, *** $p<0.001$, **** $p<0.0001$). Median + 95% confidence interval; sample size displayed above x-axis.

Unlike placebo, KY1005 led to a significant decrease in IgE, IL-13 and IL-22 serum concentrations at D113, which was maintained until D253.

Conclusion

Serum levels of IL-13, IL-22, IL-31 and IL-17A were quantified in all patients at Baseline, Days 29, 113, 169 and 253 using a combination of Olink and Simoa technology.

A significant positive correlation between baseline IL 13 and IL 22 levels and clinical score (EASI/SCORAD) was demonstrated. A positive correlation between the decrease in IL13 /IL 22 levels and decrease in clinical score at D 113 was demonstrated. In addition, a significant and specific reduction (vs baseline) in circulating IL 13 /IL 22 at D 113 in response to KY 1005 was observed. Levels of IL 13 /IL 22 remain low up to D 253 for KY 1005 treated patients.

Correlations between serum markers of AD and AD disease severity could be observed. Using linear modelling of EASI scores with serum protein levels, a significant association between disease severity and up to IL-13, IL-22, IL-17A across multiple time points could be demonstrated. These proteins positively correlated with disease severity not only at baseline, but also at later timepoints.

When treatment-induced changes in serum protein levels upon KY1005 and Placebo treatment at Day 113 were assessed IL-13, IL-22 and IL-17A were found to be significantly changed upon KY1005 treatment. These proteins were found to be affected by KY1005, but not Placebo treatment, suggesting that these proteins are specifically affected by KY1005.

5

KY1005 treatment, both low and high doses, induced a significant drop in IgE levels, which was already observable for both treatments at day 29 (and statistically significant for KY1005 low dose) and was significant for both KY1005 treatment groups at day 113.

In addition, KY1005-treated patients that were considered responders (vIGA 0-1) at Day113
10 demonstrated a significant reduction in IgE levels (vs baseline) by day 113 which continued to decrease up to day 253. Reduction in IgE levels is associated with KY1005 treatment. IgE levels may serve as a response biomarker to KY1005 treatment.

SEQUENCE LISTING

SEQ ID NO:				
1	10A07		VH Nucleotide Sequence	GAGGTGCAACTGGTGGAGTCTGGGGGAGTCTTGGTACAGCCGGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGTTAT ATTATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTC TCAGGTATTAGTGGTAGTGGTGGTGGTACATACTACGCAGACTCCATGA AGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCT GCAGATGAACAGCCTGAGAGTCGAGGACACGGCCGTATATTACTGTGC GAAAGATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTAC GGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
2			VH Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYIMTWVRQAPGKGLEWVSG ISGSGGGTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDR LGPITLVRGGYYYGMDVWGQGTTVTVSS
3			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACCTTTAGCAGTTATATT
4			HCDR1 Amino Acid Sequence (IMGT)	GFTFSSYI
5			HCDR2 Nucleotide Sequence (IMGT)	ATTAGTGGTAGTGGTGGTGGTACA
6			HCDR2 Amino Acid Sequence (IMGT)	ISGSGGGT
7			HCDR3 Nucleotide Sequence (IMGT)	GCGAAAGATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTAC TACGGTATGGACGTC
8			HCDR3 Amino Acid Sequence (IMGT)	AKDRLGPITLVRGGYYYGMDV
9			HCDR1 Nucleotide Sequence (KABAT)	AGTTATATTATGACT
10			HCDR1 Amino Acid Sequence (KABAT)	SYIMT
11			HCDR2 Nucleotide Sequence (KABAT)	GGTATTAGTGGTAGTGGTGGTGGTACATACTACGCAGACTCCATGAAG GGC
12			HCDR2 Amino Acid Sequence (KABAT)	GISGSGGGTYYADSMKG
13			HCDR3 Nucleotide Sequence (KABAT)	GATCGGTTAGGTCCGATTACTTTGGTTCGGGGGGGCTATTACTACGGTA TGGACGTC
14			HCDR3 Amino Acid Sequence (KABAT)	DRLGPITLVRGGYYYGMDV
15			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCGACTATTT AAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTAT

				GCTGCATCCAGTTTGCAAAGTGGAGTCCCATCAAGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCGTCAGCAGTCTGCAACCTGAAGA TTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCGGACGTTC GGCCAAGGGACCAGGGTGGAAATCAAA
16			VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKFLIYAA SSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQSYSTPRTFGQGT RVEIK
17			LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCGACTAT
18			LCDR1 Amino Acid Sequence (IMGT)	QSISDY
19			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
20			LCDR2 Amino Acid Sequence (IMGT)	AAS
21			LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGTTACAGTACCCCTCGGACG
22			LCDR3 Amino Acid Sequence (IMGT)	QQSYSTPRT
23			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCGACTATTTAAAT
24			LCDR1 Amino Acid Sequence (KABAT)	RASQSISDYLN
25			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
26			LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
27			LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTTACAGTACCCCTCGGACG
28			LCDR3 Amino Acid Sequence (KABAT)	QQSYSTPRT
29			Heavy Chain Nucleotide Sequence	GAGGTCCAGCTCGTGGAAAGCGGAGGAGTGCTCGTGCAGCCTGGAGGC AGCCTCAGGCTGTCCTGTGCCGCCTCCGGCTTCACCTTCAGCAGCTACA TCATGACCTGGGTGAGGCAGGCTCCCGGAAAAGGCCTGGAGTGGGTGT CCGGCATCTCCGGATCCGGAGGAGGCACATACTACGCCGACAGCATGAA GGGCCGGTTCACCATCAGCCGGGACAATAGCAAGAATACCCTCTACCTG CAAATGAACAGCCTGCGGGTGGAGGATACCGCCGTGTACTACTGCGCCA AAGATAGGCTGGGCCCCATTACCCTCGTGAGGGGAGGCTATTACTACG GCATGGATGTGTGGGGCCAGGGCACCACCGTGACAGTGTCCAGCGCCA GCACCAAGGGCCCTTCCGTGTTCCCCCTGGCCCCTTGCAGCAGGAGCAC CTCCGAATCCACAGCTGCCCTGGGCTGTCTGGTGAAGGACTACTTTCCC GAGCCCGTGACCGTGAGCTGGAACAGCGGCGCTCTGACATCCGGCGTC CACACCTTTCCTGCCGTCCTGCAGTCCTCCGGCCTCTACTCCCTGTCCTC CGTGGTGACCGTGCCTAGCTCCTCCCTCGGCACCAAGACCTACACCTGT AACGTGGACCACAAACCCTCCAACACCAAGGTGGACAAACGGGTCGAGA

				GCAAGTACGGCCCTCCCTGCCCTCCTTGTCCTGCCCCCGAGTTCGAAGG CGGACCCAGCGTGTTCCTGTTCCCTCCTAAGCCCAAGGACACCCTCATG ATCAGCCGGACACCCGAGGTGACCTGCGTGGTGGTGGATGTGAGCCAG GAGGACCCTGAGGTCCAGTTCAACTGGTATGTGGATGGCGTGGAGGTG CACAACGCCAAGACAAAGCCCCGGGAAGAGCAGTTCAACTCCACCTACA GGGTGGTCAGCGTGCTGACCGTGCTGCATCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCAGCAATAAGGGACTGCCCAGCAGCATCG AGAAGACCATCTCCAAGGCTAAAGGCCAGCCCCGGGAACCTCAGGTGTA CACCCTGCCTCCCAGCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTG ACCTGCCTGGTGAAGGGATTCTACCCTTCCGACATCGCCGTGGAGTGG GAGTCCAACGGCCAGCCCGAGAACAATTATAAGACCACCCCTCCCGTCC TCGACAGCGACGGATCCTTCTTTCTGTACTCCAGGCTGACCGTGGATAA GTCCAGGTGGCAGGAAGGCAACGTGTTCAGCTGCTCCGTGATGCACGA GGCCCTGCACAATCACTACACCCAGAAGTCCCTGAGCCTGTCCCTGGGA AAG
30			Heavy Chain Amino Acid Sequence	EVQLVESGGVLVQPGGSLRLSCAASGFTFSSYIMTWVRQAPGKGLEWVSG ISGSGGGTYYADSMKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDR LGPITLVRGGYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL GK
31			Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGTCCGCCTCCGTGGGAG ACAGGGTGACCATCACCTGCCGGGCCAGCCAGTCCATCAGCGACTACCT GAACTGGTATCAGCAGAAGCCCGGCAAGGCCCCTAAGTTCCTGATCTAC GCCGCTTCCTCCCTGCAGTCCGGAGTGCCCAGCAGGTTTTCCGGCTCCG GATCCGGCACCGACTTCACCCTGACCGTGTCCAGCCTGCAGCCCGAGGA CTTCGCCACCTACTACTGCCAGCAGAGCTACAGCACCCCCAGGACATTT GGCCAGGGCACCCGGGTGGAGATCAAGAGGACCGTCGCTGCCCCCTCC GTGTTTATCTTCCCCCCCAGCGACGAGCAGCTGAAATCCGGCACCGCCT CCGTGGTCTGCCTGCTGAATAACTTCTACCCTCGGGAGGCCAAGGTGCA GTGGAAGGTGGACAACGCCCTGCAGAGCGGAAACTCCCAGGAGAGCGT

				GACCGAGCAGGACTCCAAGGACTCCACATACTCCCTGTCCTCCACCCTG ACACTGTCCAAGGCCGATTACGAGAAGCACAAGGTGTACGCCTGCGAG GTGACCCACCAGGGACTGTCCTCCCCCGTGACCAAGTCCTTCAACCGGG GCGAGTGC
32			Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISDYLNWYQQKPGKAPKFLIYAA SSLQSGVPSRFSGSGSGTDFTLTVSSLQPEDFATYYCQQSYSTPRTFGQGT RVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
33	02D10		VH Nucleotide Sequence	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACTTTTAGCAACTAT GCCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTC TCAACTATTAGCGGAAGTGGTGGTGCCACAAGGTATGCAGACTCCGTGA AGGGCCGATTCACCATATCCAGAGACAATTCCAGGAACACGGTGTATCT GCAAATGAACAGCCTGAGAGTCGAGGACACGGCCGTTTTTTACTGTACG AAAGATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTA TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
34			VH Amino Acid Sequence	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLEWVS TISGSGGATRYADSVKGRFTISRDNSRNTVYLQMNSLRVEDTAVFYCTKD RLIMATVRGPYYYGMDVWGQGTTVTVSS
35			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTTAGCAACTATGCC
36			HCDR1 Amino Acid Sequence (IMGT)	GFTFSNYA
37			HCDR2 Nucleotide Sequence (IMGT)	ATTAGCGGAAGTGGTGGTGCCACA
38			HCDR2 Amino Acid Sequence (IMGT)	ISGSGGAT
39			HCDR3 Nucleotide Sequence (IMGT)	ACGAAAGATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACG GTATGGACGTC
40			HCDR3 Amino Acid Sequence (IMGT)	TKDRLIMATVRGPYYYGMDV
41			HCDR1 Nucleotide Sequence (KABAT)	AACTATGCCATGAAC
42			HCDR1 Amino Acid Sequence (KABAT)	NYAMN
43			HCDR2 Nucleotide Sequence (KABAT)	ACTATTAGCGGAAGTGGTGGTGCCACAAGGTATGCAGACTCCGTGAAG GGC

44			HCDR2 Amino Acid Sequence (KABAT)	TISGSGGATRYADSVKG
45			HCDR3 Nucleotide Sequence (KABAT)	GATCGGCTCATTATGGCTACGGTTCGGGGACCCTATTACTACGGTATGG ACGTC
46			HCDR3 Amino Acid Sequence (KABAT)	DRLIMATVRGPYYYGMDV
47			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTT AAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAACCTCCTGATCTAT GCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTG GATCTGAGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGA TTTTGCAACTTACTACTGTCAACAGAGTCACAGTGTCTCATTCACTTTCG GCCCTGGGACCAAAGTGGATATCAAA
48			VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAA SSLQSGVPSRFSGSGSETDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGT KVDIK
49			LCDR1 Nucleotide Sequence (IMGT)	CAGAGCATTAGCAGCTAT
50			LCDR1 Amino Acid Sequence (IMGT)	QSISSY
51			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
52			LCDR2 Amino Acid Sequence (IMGT)	AAS
53			LCDR3 Nucleotide Sequence (IMGT)	CAACAGAGTCACAGTGTCTCATTCACT
54			LCDR3 Amino Acid Sequence (IMGT)	QQSHSVSFT
55			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGAGCATTAGCAGCTATTTAAAT
56			LCDR1 Amino Acid Sequence (KABAT)	RASQSISSYLN
57			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCAGTTTGCAAAGT
58			LCDR2 Amino Acid Sequence (KABAT)	AASSLQS
59			LCDR3 Nucleotide Sequence (KABAT)	CAACAGAGTCACAGTGTCTCATTCACT
60			LCDR3 Amino Acid Sequence (KABAT)	QQSHSVSFT
61			Heavy Chain Nucleotide Sequence	GAAGTGCAACTGGTGGAGTCCGGAGGAGGCCTGGTGCAGCCTGGAGGA AGCCTGAGGCTGAGCTGTGCCGCCAGCGGCTTCACCTTCAGCAACTACG CCATGAACTGGGTGAGGCAGGCCCCTGGCAAGGGACTGGAGTGGGTCT CCACCATCAGCGGCTCCGGAGGCGCTACACGGTACGCCGATAGCGTGA AGGGCCGGTTTACCATTTCCCGGGACAACTCCCGGAACACCGTGTACCT CCAGATGAACAGCCTGAGGGTGGAGGATACCGCCGTGTTCTACTGCACC

				AAGGACAGGCTGATTATGGCCACCGTGAGGGGACCTTACTACTATGGCA TGGATGTGTGGGGCCAGGGCACAACCGTCACCGTGTCCTCCGCCTCCAC CAAGGGACCTAGCGTGTTCCCTCTCGCCCCCTGTTCCAGGTCCACAAGC GAGTCCACCGCTGCCCTCGGCTGTCTGGTGAAAGACTACTTTCCCGAGC CCGTGACCGTCTCCTGGAATAGCGGAGCCCTGACCTCCGGCGTGCACAC ATTTCCCGCCGTGCTGCAGAGCAGCGGACTGTATAGCCTGAGCAGCGT GGTGACCGTGCCCAGCTCCAGCCTCGGCACCAAAACCTACACCTGCAAC GTGGACCACAAGCCCTCCAACACCAAGGTGGACAAGCGGGTGGAGAGC AAGTACGGCCCCCCTTGCCCTCCTTGTCCTGCCCCTGAGTTCGAGGGAG GACCCTCCGTGTTCCTGTTTCCCCCCAAACCCAAGGACACCCTGATGAT CTCCCGGACACCCGAGGTGACCTGTGTGGTCGTGGACGTCAGCCAGGA GGACCCCGAGGTGCAGTTCAACTGGTATGTGGACGGCGTGGAGGTGCA CAATGCCAAAACCAAGCCCAGGGAGGAGCAGTTCAATTCCACCTACAGG GTGGTGAGCGTGCTGACCGTCCTGCATCAGGATTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTGTCCAACAAGGGACTGCCCAGCTCCATCGAGA AGACCATCAGCAAGGCTAAGGGCCAGCCGAGGGAGCCCCAGGTGTATA CCCTGCCTCCTAGCCAGGAAGAGATGACCAAGAACCAAGTGTCCCTGAC CTGCCTGGTGAAGGGATTCTACCCCTCCGACATCGCCGTGGAGTGGGA GAGCAATGGCCAGCCCGAGAACAACTACAAAACAACCCCTCCCGTGCTC GATAGCGACGGCAGCTTCTTTCTCTACAGCCGGCTGACAGTGGACAAGA GCAGGTGGCAGGAGGGCAACGTGTTCTCCTGTTCCGTGATGCACGAGG CCCTGCACAATCACTACACCCAGAAGAGCCTCTCCCTGTCCCTGGGCAA G
62			Heavy Chain Amino Acid Sequence	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLEWVS TISGSGGATRYADSVKGRFTISRDNSRNTVYLQMNSLRVEDTAVFYCTKD RLIMATVRGPYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSEST AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREE QFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPRE PQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL GK

63			Light Chain Nucleotide Sequence	GACATCCAGATGACCCAGTCCCCTTCCTCCCTGAGCGCTAGCGTGGGAG ATAGGGTGACCATCACCTGCAGGGCCTCCCAAAGCATCTCCTCCTACCT GAACTGGTACCAGCAGAAACCCGGCAAGGCCCCCAACCTGCTGATCTAC GCTGCCTCCTCCCTCCAGTCCGGCGTGCCTAGCAGGTTTAGCGGCTCCG GAAGCGAGACCGACTTCACCCTGACCATCTCCTCCCTGCAGCCCGAGGA CTTCGCCACCTACTACTGCCAGCAATCCCACAGCGTGTCCTTCACCTTCG GCCCCGGCACCAAGGTGGACATCAAGAGGACCGTGGCCGCCCCCTCCG TGTTCATCTTTCCCCCCTCCGATGAACAGCTGAAGAGCGGCACCGCTAG CGTGGTGTGCCTGCTGAACAACTTCTACCCCAGGGAGGCCAAGGTGCA GTGGAAGGTGGACAATGCCCTGCAGTCCGGCAACAGCCAGGAGAGCGT GACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGTCCTCCACCCTG ACCCTGTCCAAGGCCGACTACGAGAAGCACAAAGTGTACGCCTGCGAAG TGACCCATCAGGGCCTGAGCTCCCCCGTGACCAAGTCCTTTAACAGGGG CGAGTGC
64			Light Chain Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPNLLIYAA SSLQSGVPSRFSGSGSETDFTLTISSLQPEDFATYYCQQSHSVSFTFGPGT KVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
65	09H04		VH Nucleotide Sequence	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGG TCCCTGAGACTCTCCTGTGCAGCCTCTCGATTCACCCTCAGTGACTACT ACATGACCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTT CATACATTAGTAGTAGTGGTAATACCATATACTACGCAGACTCTGTGAA GGGCCGATTCACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTG CAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGA GAGATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTCT GGGGCCAAGGGACCACGGTCACCGTCTCCTCA
66			VH Amino Acid Sequence	QVQLVESGGGLVKPGGSLRLSCAASRFTLSDYYMTWIRQAPGKGLEWVSY ISSSGNTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDLS GSYWDYYYGMDVWGQGTTVTVSS
67			HCDR1 Nucleotide Sequence (IMGT)	CGATTCACCCTCAGTGACTACTAC
68			HCDR1 Amino Acid Sequence (IMGT)	RFTLSDYY
69			HCDR2 Nucleotide Sequence (IMGT)	ATTAGTAGTAGTGGTAATACCATA
70			HCDR2 Amino Acid Sequence (IMGT)	ISSSGNTI

71			HCDR3 Nucleotide Sequence (IMGT)	GCGAGAGATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGAC GTC
72			HCDR3 Amino Acid Sequence (IMGT)	ARDLSGSYWDYYYGMDV
73			HCDR1 Nucleotide Sequence (KABAT)	GACTACTACATGACC
74			HCDR1 Amino Acid Sequence (KABAT)	DYYMT
75			HCDR2 Nucleotide Sequence (KABAT)	TACATTAGTAGTAGTGGTAATACCATATACTACGCAGACTCTGTGAAGG GC
76			HCDR2 Amino Acid Sequence (KABAT)	YISSSGNTIYYADSVKG
77			HCDR3 Nucleotide Sequence (KABAT)	GATCTGAGTGGGAGCTACTGGGACTACTACTACGGTATGGACGTC
78			HCDR3 Amino Acid Sequence (KABAT)	DLSGSYWDYYYGMDV
79			VL Nucleotide Sequence	GCCATCCAGTTGACCCAGTCTCCATCCTCCCTGTCTACATCTGTAGGAG ACAGAGTCACCATCGCTTGCCGGGCAAGTCAGGGCATTAACAATGCTTT AGCCTGGTATCAGCAGAAACCAGGGAAAGCTCCTAAGCTCCTGATCTAT GATGCCTCCAGTTTGGAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGT GGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAG ATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTACCCTCGGACGTTC GGCCAAGGGACCAAGGTGGAAATCAAA
80			VL Amino Acid Sequence	AIQLTQSPSSLSTSVGDRVTIACRASQGINNALAWYQQKPGKAPKLLIYDA SSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPRTFGQGT KVEIK
81			LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAACAATGCT
82			LCDR1 Amino Acid Sequence (IMGT)	QGINNA
83			LCDR2 Nucleotide Sequence (IMGT)	GATGCCTCC
84			LCDR2 Amino Acid Sequence (IMGT)	DAS
85			LCDR3 Nucleotide Sequence (IMGT)	CAACAGTTTAATAGTTACCCTCGGACG
86			LCDR3 Amino Acid Sequence (IMGT)	QQFNSYPRT
87			LCDR1 Nucleotide Sequence (KABAT)	CGGGCAAGTCAGGGCATTAACAATGCTTTAGCC
88			LCDR1 Amino Acid Sequence (KABAT)	RASQGINNALA
89			LCDR2 Nucleotide Sequence (KABAT)	GATGCCTCCAGTTTGGAAAGT
90			LCDR2 Amino Acid Sequence (KABAT)	DASSLES
91			LCDR3 Nucleotide Sequence (KABAT)	CAACAGTTTAATAGTTACCCTCGGACG
92			LCDR3 Amino Acid Sequence (KABAT)	QQFNSYPRT

93	19H01		VH Nucleotide Sequence	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGG GTCCCTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACGCC TGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTT GGCCGTATTAAAAGCAAAACTGAAGGTGGGACAACAGACTACGCTGCAC CCGTGAAAGGCAGATTCACCATCTCAAGAGATGATTCAAAAAACACGCT GTATCTGCAAATGAACAGCCTGAAAACCGAGGACACAGCCGTGTATTAC TGTACCACAGATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTACTGGG GCCAGGGAACCCTGGTCACCGTCTCCTCA
94			VH Amino Acid Sequence	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVG RIKSKTEGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTT DFLWFGEFPFDYWGQGTLVTVSS
95			HCDR1 Nucleotide Sequence (IMGT)	GGATTCACTTTCAGTAACGCCTGG
96			HCDR1 Amino Acid Sequence (IMGT)	GFTFSNAW
97			HCDR2 Nucleotide Sequence (IMGT)	ATTAAAAGCAAAACTGAAGGTGGGACAACA
98			HCDR2 Amino Acid Sequence (IMGT)	IKSKTEGGTT
99			HCDR3 Nucleotide Sequence (IMGT)	ACCACAGATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTAC
100			HCDR3 Amino Acid Sequence (IMGT)	TTDFLWFGEFPFDY
101			HCDR1 Nucleotide Sequence (KABAT)	AACGCCTGGATGAGC
102			HCDR1 Amino Acid Sequence (KABAT)	NAWMS
103			HCDR2 Nucleotide Sequence (KABAT)	CGTATTAAAAGCAAAACTGAAGGTGGGACAACAGACTACGCTGCACCCG TGAAAGGC
104			HCDR2 Amino Acid Sequence (KABAT)	RIKSKTEGGTTDYAAPVKG
105			HCDR3 Nucleotide Sequence (KABAT)	GATTTTCTATGGTTCGGGGAGTTCCCTTTTGACTAC
106			HCDR3 Amino Acid Sequence (KABAT)	DFLWFGEFPFDY
107			VL Nucleotide Sequence	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAG ACAGAGTCACCATCACTTGCCGGGCGAGTCAGGGCATTAGCAATTATTT AGCCTGGTATCAGCAGAAACCAGGGAAAATTCCTAAGCTCCTGATCTAT GCTGCATCCACTTTGCAATCAGGGGTCCCATCTCGGTTCAGTGGCAGTG GATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGA TGTTGCAACTTATTACTGTCAAAAGTATAACAGTGCCCCTCGGACGTTC GGCCAAGGGACCAAGGTGGAAATCAAA

108			VL Amino Acid Sequence	DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKIPKLLIYAA STLQSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYNSAPRTFGQGT KVEIK
109			LCDR1 Nucleotide Sequence (IMGT)	CAGGGCATTAGCAATTAT
110			LCDR1 Amino Acid Sequence (IMGT)	QGISNY
111			LCDR2 Nucleotide Sequence (IMGT)	GCTGCATCC
112			LCDR2 Amino Acid Sequence (IMGT)	AAS
113			LCDR3 Nucleotide Sequence (IMGT)	CAAAAGTATAACAGTGCCCCTCGGACG
114			LCDR3 Amino Acid Sequence (IMGT)	QKYNSAPRT
115			LCDR1 Nucleotide Sequence (KABAT)	CGGGCGAGTCAGGGCATTAGCAATTATTTAGCC
116			LCDR1 Amino Acid Sequence (KABAT)	RASQGISNYLA
117			LCDR2 Nucleotide Sequence (KABAT)	GCTGCATCCACTTTGCAATCA
118			LCDR2 Amino Acid Sequence (KABAT)	AASTLQS
119			LCDR3 Nucleotide Sequence (KABAT)	CAAAAGTATAACAGTGCCCCTCGGACG
120			LCDR3 Amino Acid Sequence (KABAT)	QKYNSAPRT
121	Human IgG4 heavy chain constant region #1	IGHG *01	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagca cagccgccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaact caggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactc cctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgt agatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtccccccat gcccatcatgcccagcacctgagttcctgggggggaccatcagtcttcctgttcccccaaaaccc aaggacactctcatgatctcccggaccccctgaggtcacgtgcgtggtggtggacgtgagccag gaagaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaagac aaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgc accaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgtcc tccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccct gcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggct tctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaggctaaccgtggac aagagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaac cactacacacagaagagcctctccctgtctctgggtaaa

122			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK
123	Human IgG4 heavy chain constant region #2	IGHG *02	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagca cagccgccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaact caggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactc cctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgt agatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtcccccgt gcccatcatgcccagcacctgagttcctgggggggaccatcagtcttcctgttcccccaaaaccc aaggacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtggacgtgagccag gaagaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaagac aaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgtcgtgc accaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgtcc tccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccct gccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggct tctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaggctaaccgtggac aagagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaac cactacacgcagaagagcctctccctgtctctgggtaaa
124			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVVHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK

125	Human IgG4 heavy chain constant region #3	IGHG *03	Heavy Chain Constant Region Nucleotide Sequence	gcttccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagca cagccgccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaact caggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactc cctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacctacacctgcaacgt agatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtcccccat gcccatcatgcccagcacctgagttcctgggggggaccatcagtcttcctgttcccccaaaaccc aaggacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtggacgtgagccag gaagaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaagac aaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgtcctgc accaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgtcc tccatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtacaccct gcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggct tctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaa gaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggac aagagcaggtggcaggaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaa ccactacacgcagaagagcctctccctgtctctgggtaaa
126			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK
127	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version A	gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagc acggccgccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaac tcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacctacacctgcaac gtagatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtccccc atgcccaccatgcccagcgcctgaatttgaggggggaccatcagtcttcctgttcccccaaaa cccaaggacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtggacgtgagc caggaagaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaa gacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgtcc tgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctccc gtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtac accctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaa

				aggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgcctcccgtgctggactccgacggatccttcttcctctacagcaggctaaccgt ggacaagagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgc acaaccactacacacagaagagcctctccctgtctctgggtaaa
128	IgG4 heavy chain constant region --IgG4-PE		Heavy Chain Constant Region Amino Acid Sequence - Encoded by Synthetic Version A, B & C	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK
129	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version B	Gcctccaccaagggacctagcgtgttccctctcgcccccctgttccaggtccacaagcgagtcca ccgctgcccctcggctgtctggtgaaagactactttcccgagcccgtgaccgtctcctggaatagc ggagccctgacctccggcgtgcacacatttcccgccgtgctgcagagcagcggactgtatagc ctgagcagcgtggtgaccgtgcccagctccagcctcggcaccaaaacctacacctgcaacgtg gaccacaagccctccaacaccaaggtggacaagcgggtggagagcaagtacggccccctt gccctccttgtcctgcccctgagttcgagggaggaccctccgtgttcctgtttccccccaaaccca aggacaccctgatgatctcccggacacccgaggtgacctgtgtggtcgtggacgtcagccag gaggaccccgaggtgcagttcaactggtatgtggacggcgtggaggtgcacaatgccaaaa ccaagcccagggaggagcagttcaattccacctacagggtggtgagcgtgctgaccgtcctg catcaggattggctgaacggcaaggagtacaagtgcaaggtgtccaacaagggactgccca gctccatcgagaagaccatcagcaaggctaagggccagccgagggagccccaggtgtatac cctgcctcctagccaggaagagatgaccaagaaccaagtgtccctgacctgcctggtgaagg gattctacccctccgacatcgccgtggagtgggagagcaatggccagcccgagaacaactac aaaacaacccctcccgtgctcgatagcgacggcagcttctttctctacagccggctgacagtgg acaagagcaggtggcaggagggcaacgtgttctcctgttccgtgatgcacgaggccctgcac aatcactacacccagaagagcctctccctgtccctgggcaag

130	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version C	gccagcaccaagggcccttccgtgttccccctggcccctttgcagcaggagcacctccgaatcc acagctgccctgggctgtctggtgaaggactactttcccgagcccgtgaccgtgagctggaac agcggcgctctgacatccggcgtccacacctttcctgccgtcctgcagtcctccggcctctactcc ctgtcctccgtggtgaccgtgcctagctcctccctcggcaccaagacctacacctgtaacgtgga ccacaaaccctccaacaccaaggtggacaaacgggtcgagagcaagtacggccctccctgcc ctccttgtcctgcccccgagttcgaaggcggacccagcgtgttcctgttccctcctaagcccaag gacaccctcatgatcagccggacacccgaggtgacctgcgtggtggtggatgtgagccagga ggaccctgaggtccagttcaactggtatgtggatggcgtggaggtgcacaacgccaagacaa agccccgggaagagcagttcaactccacctacagggtggtcagcgtgctgaccgtgctgcatc aggactggctgaacggcaaggagtacaagtgcaaggtcagcaataagggactgcccagca gcatcgagaagaccatctccaaggctaaaggccagccccgggaacctcaggtgtacaccctg cctcccagccaggaggagatgaccaagaaccaggtgagcctgacctgcctggtgaagggat tctacccttccgacatcgccgtggagtgggagtccaacggccagcccgagaacaattataaga ccacccctcccgtcctcgacagcgacggatccttctttctgtactccaggctgaccgtggataag tccaggtggcaggaaggcaacgtgttcagctgctccgtgatgcacgaggccctgcacaatca ctacacccagaagtccctgagcctgtccctgggaaag
131	IgG4 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence - Synthetic Version D	gcctccaccaagggcccatccgtcttccccctggcgccctgctccaggagcacctccgagagc acggccgccctgggctgcctggtcaaggactacttccccgaaccagtgacggtgtcgtggaac tcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacgaagacctacacctgcaac gtagatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtccccc atgcccaccatgcccagcgcctccagttgcgggggggaccatcagtcttcctgttcccccaaaa cccaaggacactctcatgatctcccggacccctgaggtcacgtgcgtggtggtggacgtgagc caggaagaccccgaggtccagttcaactggtacgtggatggcgtggaggtgcataatgccaa gacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgtcc tgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctccc gtcatcgatcgagaaaaccatctccaaagccaaagggcagccccgagagccacaggtgtac accctgcccccatcccaggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaa aggcttctaccccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaac tacaagaccacgcctcccgtgctggactccgacggatccttcttcctctacagcaggctaaccgt ggacaagagcaggtggcaggaggggaatgtcttctcatgctccgtgatgcatgaggctctgc acaaccactacacacagaagagcctctccctgtctctgggtaaa
132			Heavy Chain Constant Region Amino Acid Sequence - encoded by Synthetic Version D	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKY GPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV

				QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVF SCSVMHEALHNHYTQKSLSLSLGK
133	Human IgG1 heavy chain constant region		Heavy Chain Constant Region Nucleotide Sequence	gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggca cagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaact caggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactc cctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgt gaatcacaagcccagcaacaccaaggtggacaagaaagtggagcccaaatcttgtgacaaaa actcacacatgcccaccgtgcccagcacctgaactcgcgggggcaccgtcagtcttcctcttcc ccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtgg acgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcat aatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgtggtcagcgtcc tcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaa gccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccac aggtgtacaccctgcccccatcccgggatgagctgaccaagaaccaggtcagcctgacctgcc tggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccgga gaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaag ctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatga ggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
134			Heavy Chain Constant Region Amino Acid Sequence	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS CDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
135	Human Cκ constant region	IGKC *01	Cκ Light Chain Constant Region Nucleotide Sequence	cgtacggtggccgctccctccgtgttcatcttcccaccttccgacgagcagctgaagtccggcac cgcttctgtcgtgtgcctgctgaacaacttctacccccgcgaggccaaggtgcagtggaaggtg gacaacgccctgcagtccggcaactcccaggaatccgtgaccgagcaggactccaaggaca gcacctactccctgtcctccaccctgaccctgtccaaggccgactacgagaagcacaaggtgta cgcctgcgaagtgacccaccagggcctgtctagccccgtgaccaagtctttcaaccggggcga gtgt

136			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
137	Human Cκ constant region	IGKC *02	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaact gcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtgg ataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggagagcaaggacag cacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtct acgccggcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacagggg agagtgt
138			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQESKDSTYSLSSTLTLSKADYEKHKVYAGEVTHQGLSSPVTKS FNRGEC
139	Human Cκ constant region	IGKC *03	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaact gcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagcggaaggtg gataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggagagcaaggaca gcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagt ctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggg gagagtgt
140			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQRKVDNALQSGN SQESVTEQESKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC
141	Human Cκ constant region	IGKC *04	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaact gcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtgg ataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacag cacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaactct acgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacagggga gagtgt
142			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKLYACEVTHQGLSSPVTKS FNRGEC
143	Human Cκ constant region	IGKC *05	Cκ Light Chain Constant Region Nucleotide Sequence	cgaactgtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaact gcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtgg ataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacag cacctacagcctcagcaacaccctgacgctgagcaaagcagactacgagaaacacaaagtct

				acgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacagggga gagtgc
144			Cκ Light Chain Constant Region Amino Acid Sequence	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSNTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
145	Human Cλ constant region	IGCλ1 *01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggccaaccccacggtcactctgttcccgccctcctctgaggagctccaagccaacaag gccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcttggaaggca gatggcagccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagcaacaac aagtacgcggccagcagctacctgagcctgacgcccgagcagtggaagtcccacagaagct acagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctacagaatg ttca
146			Cλ Light Chain Constant Region Amino Acid Sequence	PKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGV ETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPT ECS
147	Human Cλ constant region	IGCλ1 *02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagcca acaaggccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctgga aggcagatggcagccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagca acaacaagtacgcggccagcagctacctgagcctgacgcccgagcagtggaagtcccacag aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctaca gaatgttca
148			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKA GVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVA PTECS
149	Human Cλ constant region	IGCλ2 *01	Cλ Light Chain Constant Region Nucleotide Sequence - Version A	ggtcagcccaaggccaaccccactgtcactctgttcccgccctcctctgaggagctccaagcca acaaggccacactagtgtgtctgatcagtgacttctacccgggagctgtgacagtggcctgga aggcagatggcagccccgtcaaggcgggagtggagaccaccaaaccctccaaacagagca acaacaagtacgcggccagcagctacctgagcctgacgcccgagcagtggaagtcccacag aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctaca gaatgttca
150			Cλ Light Chain Constant Region Nucleotide Sequence - Version B	ggccagcctaaggccgctccttctgtgaccctgttcccccatcctccgaggaactgcaggcta acaaggccaccctcgtgtgcctgatcagcgacttctaccctggcgccgtgaccgtggcctgga aggctgatagctctcctgtgaaggccggcgtggaaaccaccacccctccaagcagtccaaca acaaatacgccgcctcctcctacctgtccctgaccctgagcagtggaagtcccaccggtccta

				cagctgccaagtgacccacgagggctccaccgtggaaaagaccgtggctcctaccgagtgctcc
151			Cλ Light Chain Constant Region Nucleotide Sequence - Version C	ggccagcctaaagctgcccccagcgtcaccctgtttcctccctccagcgaggagctccaggccaacaaggccaccctcgtgtgcctgatctccgacttctatcccggcgctgtgaccgtggcttggaaagccgactccagccctgtcaaagccggcgtggagaccaccacaccctccaagcagtccaacaacaagtacgccgcctccagctatctctccctgaccctgagcagtggaagtcccaccggtcctactcctgtcaggtgacccacgagggctccaccgtggaaaagaccgtcgccccaccgagtgctcc
152			Cλ Light Chain Constant Region Amino Acid Sequence - Encoded by Version A, B & C	GQPKANPTVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
153	Human Cλ constant region	IGCλ2 *02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgcccccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctggaaggcagatagcagccccgtcaaggcgggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagcagctatctgagcctgacgcctgagcagtggaagtcccacagaagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctacagaatgttca
154			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
155	Human Cλ constant region	IGCλ3 *01	Cλ Light Chain Constant Region Nucleotide Sequence	cccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctacccgggagccgtgacagttgcctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagcagctacctgagcctgacgcctgagcagtggaagtcccacaaaagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagttgcccctacggaatgttca
156			Cλ Light Chain Constant Region Amino Acid Sequence	PKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVAPTECS
157	Human Cλ constant region	IGCλ3 *02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgcccccctcggtcactctgttcccaccctcctctgaggagcttcaagccaacaaggccacactggtgtgtctcataagtgacttctacccggggccagtgacagttgcctggaaggcagatagcagccccgtcaaggcgggggtggagaccaccacaccctccaaacaaagcaacaacaagtacgcggccagcagctacctgagcctgacgcctgagcagtggaagtcccacaa

				aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctacg gaatgttca
158			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGPVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVA PTECS
159	Human Cλ constant region	IGCλ3 *03	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccaccctcctctgaggagcttcaagcca acaaggccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctgga aggcagatagcagccccgtcaaggcgggagtggagaccaccacaccctccaaacaaagca acaacaagtacgcggccagcagctacctgagcctgacgcctgagcagtggaagtcccacaa aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctaca gaatgttca
160			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVEKTVA PTECS
161	Human Cλ constant region	IGCλ3 *04	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccctcggtcactctgttcccgccctcctctgaggagcttcaagcca acaaggccacactggtgtgtctcataagtgacttctacccgggagccgtgacagtggcctgga aggcagatagcagccccgtcaaggcgggagtggagaccaccacaccctccaaacaaagca acaacaagtacgcggccagcagctacctgagcctgacgcctgagcagtggaagtcccacag aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctaca gaatgttca
162			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKA GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVA PTECS
163	Human Cλ constant region	IGCλ6 *01	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccgccctcctctgaggagcttcaagcca acaaggccacactggtgtgcctgatcagtgacttctacccgggagctgtgaaagtggcctgga aggcagatggcagccccgtcaacacgggagtggagaccaccacaccctccaaacagagca acaacaagtacgcggccagcagctacctgagcctgacgcctgagcagtggaagtcccacag aagctacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggcccctgca gaatgttca
164			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNT GVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVA PAECS

165	Human Cλ constant region	IGCλ7 *02	Cλ Light Chain Constant Region Nucleotide Sequence	ggtcagcccaaggctgccccatcggtcactctgttcccaccctcctctgaggagcttcaagcca acaaggccacactggtgtgtctcgtaagtgacttctacccgggagccgtgacagtggcctgga aggcagatggcagccccgtcaaggtgggagtggagaccaccaaaccctccaaacaaagca acaacaagtatgcggccagcagctacctgagcctgacgcccgagcagtggaagtcccacag aagctacagctgccgggtcacgcatgaagggagcaccgtggagaagacagtggcccctgca gaatgctct
166			Cλ Light Chain Constant Region Amino Acid Sequence	GQPKAAPSVTLFPPSSEELQANKATLVCLVSDFYPGAVTVAWKADGSPVKV GVETTKPSKQSNNKYAASSYLSLTPEQWKSHRSYSCRVTHEGSTVEKTVA PAECS
167	Recombinant Human OX40L (Leader sequence, Isoleucine Zipper and FLAG Sequence Included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCG TGCACAGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGA AGATAAAATTGAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAA ATTGCGCGTATCAAAAAGCTGATTGGCGAACGTGGCGGTGGCAGCGGT GGCGGTAGCGGCGGTGGCAGCCAGGTGTCCCACCGATACCCCAGGATC CAGTCCATCAAGGTCCAGTTCACCGAGTACAAAAAGGAGAAGGGATTCA TCCTGACCTCCCAAAAGGAGGACGAGATCATGAAGGTGCAAAACAACTC CGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCCTGAAGGGCTAC TTCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACGAGGAGC CCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATTCCCTGATGGTGGC CAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACCACCGACAAC ACCAGCCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCTGATCC ATCAGAACCCCGGCGAGTTTTGCGTCCTG
168			Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIAR IKKLIGERGGGSGGGSGGGSQVSHRYPRIQSIKVQFTEYKKEKGFILTSQK EDEIMKVQNNSVIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVR SVNSLMVASLTYKDKVYLNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
169	Recombinant Rhesus OX40L (Leader Sequence, FLAG and Isoleucine zipper included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCG TGCACAGCGATTACAAGGATGACGACGATAAGCGTATGAAACAGATCGA AGATAAAATTGAAGAGATCTTGAGCAAAATCTATCATATCGAAAACGAA ATTGCGCGTATCAAAAAGCTGATTGGCGAACGTGGCGGTGGCAGCGGT GGCGGTAGCGGCGGTGGCAGCCAGGTGTCCCACCAATACCCCAGGATC CAGTCCATCAAGGTCCAGTTCACCGAGTACAAAAAGGAGGAGGGATTCA TCCTGACCTCCCAAAAGGAGGACGAGATCATGAAGGTGCAAAACAACTC CGTGATCATCAACTGCGACGGCTTCTACCTGATCTCCCTGAAGGGCTAC TTCTCCCAGGAGGTGAACATCTCCCTGCACTACCAGAAGGACGAGGAGC

				CCCTGTTCCAGCTGAAGAAGGTGAGGTCCGTGAATTCCCTGATGGTGGC CAGCCTGACCTACAAGGACAAGGTCTACCTGAACGTGACCACCGACAAC ACCAGCCTGGACGACTTCCATGTCAACGGCGGCGAGCTGATCCTGATCC ATCAGAACCCCGGCGAGTTTTGCGTCCTG
170			Amino Acid Sequence	MGWSCIILFLVATATGVHSDYKDDDDKRMKQIEDKIEEILSKIYHIENEIAR IKKLIGERGGGSGGGSGGGSQVSHQYPRIQSIKVQFTEYKKEEGFILTSQK EDEIMKVQNNSVIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVR SVNSLMVASLTYKDKVYLNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
171	Recombinant Human OX40R (Leader Sequence and Human Fc Sequence included)		Nucleotide Sequence	ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCCACCGCCACCGGCG TGCACAGCCTGCATTGCGTGGGCGACACCTATCCCTCCAACGACAGGTG CTGCCACGAGTGCAGGCCTGGAAACGGCATGGTGAGCAGGTGCAGCCG GTCCCAGAATACCGTGTGTAGGCCCTGCGGCCCCGGCTTTTACAACGAC GTGGTGTCCTCCAAGCCCTGCAAGCCCTGCACATGGTGCAACCTGCGGT CCGGCAGCGAGAGGAAGCAGCTCTGCACAGCCACCCAGGACACCGTCT GTAGGTGTAGGGCTGGCACCCAGCCTCTGGACTCCTACAAGCCCGGCG TGGATTGTGCTCCTTGCCCTCCCGGCCATTTCTCCCCTGGCGACAACCA GGCTTGCAAGCCCTGGACCAACTGTACCCTGGCCGGCAAGCATACACTG CAGCCTGCTTCCAACTCCTCCGACGCTATCTGCGAGGATAGGGACCCCC CTGCCACACAACCCCAGGAGACACAGGGCCCTCCTGCTAGGCCCATCAC AGTCCAACCCACCGAAGCCTGGCCCAGGACATCCCAAGGCCCTTCCACC AGGCCTGTGGAAGTGCCTGGAGGAAGGGCTGTGGCCATTGAAGGTCGT ATGGATGAACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTC CTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAA GCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTGACCTGCGTG GTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGTAC GTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAA CAGTACAACTCCACCTACCGGGTGGTGTCCGTGCTGACCGTGCTGCACC AGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGG CCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCC CCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACC AAGAACCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCG ATATCGCCGTGGAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAA

				GACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTCTTCCTGTACAGC AAGCTGACAGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTGTTCTCC TGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCC TGTCCCTGAGCCCCTGA
172			Amino Acid Sequence	MGWSCIILFLVATATGVHSLHCVGDTYPSNDRCCHECRPGNGMVSRCSRS QNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLCTATQDTVCR CRAGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCTLAGKHTLQP ASNSSDAICEDRDPPATQPQETQGPPARPITVQPTEAWPRTSQGPSTRPV EVPGGRAVAIEGRMDEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
173	Cell Expressed OX40L (CHO/MEF) (Leader sequence included)		Nucleotide Sequence	ATGGAGAGGGTGCAGCCCCTCGAGGAGAACGTGGGAAACGCCGCCAGG CCTAGGTTCGAGAGGAACAAGCTGCTGCTGGTGGCTTCCGTGATCCAA GGACTCGGCCTGCTGCTCTGCTTCACCTACATCTGCCTCCACTTCAGCG CCCTGCAGGTGTCCCACCGATACCCCAGGATCCAGTCCATCAAGGTCCA GTTCACCGAGTACAAAAAGGAGAAGGGATTCATCCTGACCTCCCAAAAG GAGGACGAGATCATGAAGGTGCAAAACAACTCCGTGATCATCAACTGCG ACGGCTTCTACCTGATCTCCCTGAAGGGCTACTTCTCCCAGGAGGTGAA CATCTCCCTGCACTACCAGAAGGACGAGGAGCCCCTGTTCCAGCTGAAG AAGGTGAGGTCCGTGAATTCCCTGATGGTGGCCAGCCTGACCTACAAG GACAAGGTCTACCTGAACGTGACCACCGACAACACCAGCCTGGACGACT TCCATGTCAACGGCGGCGAGCTGATCCTGATCCATCAGAACCCCGGCGA GTTTTGCGTCCTGTAA
174			Amino Acid Sequence	MERVQPLEENVGNAARPRFERNKLLLVASVIQGLGLLLCFTYICLHFSALQV SHRYPRIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQNNSVIINCDGFYLISL

				KGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLNVTTD NTSLDDFHVNGGELILIHQNPGEFC
175	Cell Expressed OX40 receptor (HT1080)		Nucleotide Sequence	ATGTGCGTGGGGGCTCGGCGGCTGGGCCGCGGGCCGTGTGCGGCTCT GCTCCTCCTGGGCCTGGGGCTGAGCACCGTGACGGGGCTCCACTGTGT CGGGGACACCTACCCCAGCAACGACCGGTGCTGCCACGAGTGCAGGCC AGGCAACGGGATGGTGAGCCGCTGCAGCCGCTCCCAGAACACGGTGTG CCGTCCGTGCGGGCCGGGCTTCTACAACGACGTGGTCAGCTCCAAGCC GTGCAAGCCCTGCACGTGGTGTAACCTCAGAAGTGGGAGTGAGCGGAA GCAGCTGTGCACGGCCACACAGGACACAGTCTGCCGCTGCCGGGCGGG CACCCAGCCCCTGGACAGCTACAAGCCTGGAGTTGACTGTGCCCCCTGC CCTCCAGGGCACTTCTCCCCAGGCGACAACCAGGCCTGCAAGCCCTGGA CCAACTGCACCTTGGCTGGGAAGCACACCCTGCAGCCGGCCAGCAATAG CTCGGACGCAATCTGTGAGGACAGGGACCCCCCAGCCACGCAGCCCCAG GAGACCCAGGGCCCCCCGGCCAGGCCCATCACTGTCCAGCCCACTGAAG CCTGGCCCAGAACCTCACAGGGACCCTCCACCCGGCCCGTGGAGGTCCC CGGGGGCCGTGCGGTTGCCGCCATCCTGGGCCTGGGCCTGGTGCTGGG GCTGCTGGGCCCCCTGGCCATCCTGCTGGCCCTGTACCTGCTCCGGAG GGACCAGAGGCTGCCCCCCGATGCCCACAAGCCCCCTGGGGGAGGCAG TTTCCGGACCCCCATCCAAGAGGAGCAGGCCGACGCCCACTCCACCCTG GCCAAGATCTGA
176			Amino Acid Sequence	MCVGARRLGRGPCAALLLLGLGLSTVTGLHCVGDTYPSNDRCCHECRPGN GMVSRCSRSQNTVCRPCGPGFYNDVVSSKPCKPCTWCNLRSGSERKQLC TATQDTVCRCRAGTQPLDSYKPGVDCAPCPPGHFSPGDNQACKPWTNCT LAGKHTLQPASNSSDAICEDRDPPATQPQETQGPPARPITVQPTEAWPRT SQGPSTRPVEVPGGRAVAAILGLGLVLGLLGPLAILLALYLLRRDQRLPPDA HKPPGGGSFRTPIQEEQADAHSTLAKI
177	OX40L15B07		Amino Acid Sequence of OX40L15B07 (Seq ID No 179 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELVAT ITGGSSINYGDFVKGRFTISIDNAKNTVYLQMNNLKPEDTAVYYCNFNKYV TSRDTWGQGTQVTVSS
178	OX40L01B11		Amino Acid Sequence of OX40L01B11 (Seq ID No 180 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCVASGRSFSTYIMGWFRQAPGKEREFVATI SRSGITIRSADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAGPYV EQTLGLYQTLG PWDYWGQGTQVTVSS

179	OX40L01E07		Amino Acid Sequence of OX40L01E07 (Seq ID No 181 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGRTFSSIYAKGWFRQAPGKEREFVAA ISRSGRSTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAVGG ATTVTASEWDYWGLGTQVTVSS
180	OX40L01E10		Amino Acid Sequence of OX40L01E10 (Seq ID No 182 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGDSLRLSCAASGLTFSSFAMGWFRQAPGKEREFVAA ISRSGYGTSEADSVRDRFIISRDNAKNTVTLHLSRLKPEDTAVYYCAAEHTL GRPSRSQINYLYWGQGTQVTVSS
181	OX40L18E09		Amino Acid Sequence of OX40L18E09 (Seq ID No 183 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASRNILSLNTMGWYRHAPGKPRELVARI SSNSKTDYADSVKGRFTISRDNAKNTVLLQMNSLKPEDTGVYYCNLNVWR TSSDYWGQGTQVTVSS
182	OX40L19A07		Amino Acid Sequence of OX40L19A07 (Seq ID No 184 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSRI KISNGRTTYAGSVKGRFTISSDNAKNTVYLQMNSLNAEDTAVYYCAADRSS LLFGSNWDRKARYDYWGQGTQVTVSS
183	OX40L19D08		Amino Acid Sequence of OX40L19D08 (Seq ID No 185 in WO2011/073180, Table A-1)	EVQLVESGGGLVQAGASLRLSCAASGRRFISNYAMGWFRQAPGQERAFVA AISRSGSITYYTDSVKGRFSISRDYAKSTVYLQMDNLKPEDTAVYYCAADG GAVRDLTTNLPDYWGRGTQVTVSS
184	OX40L075		Amino Acid Sequence of OX40L075 (Seq ID No 199 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASGRSFSTYIMGWFRQAPGKEREFVATI SRSGITTRSADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCAAGPYV EQTLG LYQTLGPWDYWGQGTLVTVSS
185	OX40L024		Amino Acid Sequence of OX40L024 (Seq ID No 200 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
186	OX40L025		Amino Acid Sequence of OX40L025 (Seq ID No 201 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
187	OX40L026		Amino Acid Sequence of OX40L026 (Seq ID No 202 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS

188	OX40L027		Amino Acid Sequence of OX40L027 (Seq ID No 203 in WO2011/073180, Table A-2)	EVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
189	OX40L028		Amino Acid Sequence of OX40L028 (Seq ID No 204 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KEREFV AAISRSG RSTSYADSVKG RFTISRD NAKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGLGTLVTVSS
190	OX40L039		Amino Acid Sequence of OX40L039 (Seq ID No 205 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASG RTFSSIYAKGWFRQAPG KERE FV AAISRSG RSTSYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCAA VGGATTVTASEWDYWGQGTLVTVSS
191	OX40L030		Amino Acid Sequence of OX40L030 (Seq ID No 206 in WO2011/073180, Table A-2)	DVQLVESGGGLVQAGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISID NAKNTVYLQM N N LKPEDTAVYYCN FN KYVTSRDTWGQGTQVTVSS
192	OX40L040		Amino Acid Sequence of OX40L040 (Seq ID No 207 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
193	OX40L041		Amino Acid Sequence of OX40L041 (Seq ID No 208 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHATGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
194	OX40L042		Amino Acid Sequence of OX40L042 (Seq ID No 209 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
195	OX40L043		Amino Acid Sequence of OX40L043 (Seq ID No 210 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGKPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
196	OX40L044		Amino Acid Sequence of OX40L044 (Seq ID No 211 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGEPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN

				KYVTSRDTWGQGTLVTVSS
197	OX40L045		Amino Acid Sequence of OX40L045 (Seq ID No 212 in WO2011/073180, Table A-2)	DVQLVESGGG LVQPGGSLRLSCAASRSIG RLD RMGWYRHATG KPRE LV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
198	OX40L046		Amino Acid Sequence of OX40L046 (Seq ID No 213 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
199	OX40L047		Amino Acid Sequence of OX40L047 (Seq ID No 214 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHAPGKPRELV ATITGGSSINYG D FVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
200	OX40L048		Amino Acid Sequence of OX40L048 (Seq ID No 215 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYADFVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
201	OX40L049		Amino Acid Sequence of OX40L049 (Seq ID No 216 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG DSVKG RFTISRDNSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
202	OX40L050		Amino Acid Sequence of OX40L050 (Seq ID No 217 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
203	OX40L053		Amino Acid Sequence of OX40L053 (Seq ID No 218 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYGDFVKGRFTISIDNSKNTVYLQM NSLRPEDTAVYYCN FNK YVTS RDTWGQGTLVTVSS
204	OX40L054		Amino Acid Sequence of OX40L054 (Seq ID No 219 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYG D FVKG RFTISRDNAKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS

205	OX40L055		Amino Acid Sequence of OX40L055 (Seq ID No 220 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRTGEPRELV ATITGGSSINYGDFVKGRFTISRDNSKNTVYLQM NN LRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
206	OX40L056		Amino Acid Sequence of OX40L056 (Seq ID No 221 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISRD NSKNTVYLQM NSLRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
207	OX40L069		Amino Acid Sequence of OX40L069 (Seq ID No 222 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISI DNSKNTVYLQM NSLRPE DTAVYYCN FN K YVTS RDTWGQGTLVTVSS
208	OX40L070		Amino Acid Sequence of OX40L070 (Seq ID No 223 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISRD NSKNTVYLQM N N LRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
209	OX40L071		Amino Acid Sequence of OX40L071 (Seq ID No 224 in WO2011/073180, Table A-2)	DVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYADSVKG RFTISI DNSKNTVYLQM N N LRPEDTAVYYCN FN KYVTSRDTWGQGTLVTVSS
210	OX40L082		Amino Acid Sequence of OX40L082 (Seq ID No 225 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGEPRELVA TITGGSSINYGDSVKGRFTISIDNSKNTVYLQM NSLRPEDTAVYYCNFNKY VTS RDTWGQGTLVTVSS
211	OX40L083		Amino Acid Sequence of OX40L083 (Seq ID No 226 in WO2011/073180, Table A-2)	EVQLVESGGGLVQPGGSLRLSCAASRSIGRLDRMGWYRHRPGKPRELV ATITGGSSINYGDSVKGRFTISIDNSKNTVYLQMNSLRPEDTAVYYCN FNK YVTS RDTWGQGTLVTVSS
212	OX40L benchmark antibody heavy chain		Amino acid sequence of OX40L benchmark antibody heavy chain (Seq ID No:177 in WO2011/073180, Table A-5)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEW VSIISGSGG FTYYADSVKG RFTISRDNSRTTLYLQM NSLRAEDTAVYYCA KDRLVAPGTFDYWGQGALVTVSSASTKG PSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSL GTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLF P PKPKDTLM IS RTPEVTCVVVDVSH E D P EVKFNWYVDGVEVH NAKTKP REEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSN KALPAPI EKTISKAKG

				QPREPQVYTLPPSRDELTKNQVSLTCLVKG FYPSDIAVEWESNGQPE N N YKTTPPVLDSDGSFFLYSKLTVD KSRWQQG NVFSCSVM H EALH N HYTQ KSLSLSPGK
213	OX40L benchmark antibody light chain		Amino acid sequence of OX40L benchmark antibody light chain (Seq ID No:178 in WO2011/073180, Table A-5)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLTISSLQPED FATYYCQQYNSYPYTFG QGTKLEIKRTVAAPSVFIFPPSD EQLKSGTASVVCLLN N FYPREAKVQWK VDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTH QGLSSPVTKSFNRGEC
214	κ light chain variable region of LC.001		Amino acid sequence of kappa light chain variable region of LC.001 (Seq ID No: 1 in WO2006/029879)	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAA SSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPYTFGQGT KLEIK
215	γ heavy chain variable region of LC.001		Amino acid sequence of γ heavy chain variable region of LC.001 (Seq ID No: 2 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFNSYAMSWVRQAPGKGLEWVSI ISGSGGFTYYADSVKGRFTISRDNSRTTLYLQMNSLRAEDTAVYYCAKDRL VAPGTFDYWGQGALVTVSS
216	κ light chain variable region of LC.005		Amino acid sequence of kappa light chain variable region of LC.005 (Seq ID No: 3 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLLIYG ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTK VDIK
217	γ heavy chain variable region of LC.005		Amino acid sequence of γ heavy chain variable region of LC.005 (Seq ID No: 4 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVA AIWYDGHDKYYSYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARD SSSWYRYFDYWGQGTLVTVSS
218	κ light chain variable region of LC.010		Amino acid sequence of kappa light chain variable region of LC.010 (Seq ID No: 5 in WO2006/029879)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGA SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSFTFGPGTKV DIK
219	γ heavy chain variable region of LC.010		Amino acid sequence of γ heavy chain variable region of LC.010 (Seq ID No: 6 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVA AIWYDGHDKYYAYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARD SSSWYRYFDYWGQGTLVTVSS
220	κ light chain variable region of LC.029		Amino acid sequence of kappa light chain variable region of LC.029 (Seq ID No: 7 in WO2006/029879)	MLHPLCKVGSHQGSVAVDLGQISLSPSAACSLKILQLITVNSIIVSLTFGGGT KVEIK

221	γ heavy chain variable region of LC.029		Amino acid sequence of γ heavy chain variable region of LC.029 (Seq ID No: 8 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWVA AIWYDGHDKYYSYYVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCARD SSSWYRYFDYWGQGTLVTVSS
222	κ light chain variable region of LC.019		Amino acid sequence of kappa light chain variable region of LC.019 (Seq ID No: 9 in WO2006/029879)	MPPVWKVGSHQGSAAVDLGQISLSPSAACSLKILQLITVNSLIVTLTFGGGT KVEIK
223	γ heavy chain variable region of LC.019		Amino acid sequence of γ heavy chain variable region of LC.019 (Seq ID No: 10 in WO2006/029879)	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYTMHWVRQAPGKGLEWVA VIWYDGSNKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARK NWSFDFWGQGTLVTVSS
224	κ light chain variable region of LC.033		Amino acid sequence of kappa light chain variable region of LC.033 (Seq ID No: 11 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQGVSRYLAWYQQKPGQAPRLLIYDA SNRATGIPARVSGSGPGTDFTLTISSLEPEDFAVDYCQQRSNWQYTFGQG TKLEI
225	γ heavy chain variable region of LC.033		Amino acid sequence of γ heavy chain variable region of LC.033 (Seq ID No: 12 in WO2006/029879)	QKQLVEFGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVA VIWNDGSNKYYVDSVKGRFIISRDNSKNTLYLQMNSLRAEDTAVYYCARD RMGIYYYGMDVWGQGTTVTVSS
226	mutant κ light chain variable region of LC.033		Amino acid sequence of mutant kappa light chain variable region of LC.033 (Seq ID No: 16 in WO2006/029879)	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDAS NRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWTFGQGTKVE I
227	γ heavy chain variable region of LC.059		Amino acid sequence of γ heavy chain variable region of LC.059 (Seq ID No: 17 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSI ISGSGGFTYYADSVKGRFTISRDNSKNTLYLQMNRLRAEDTAIYFCAKDDI PAAGTFDPWGQGTLVTVSS
228	κ light chain variable region of LC.060		Amino acid sequence of kappa light chain variable region of LC.060 (Seq ID No: 18 in WO2006/029879)	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDVS SLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYWTFGQGTKV EIK
229	γ heavy chain variable region of LC.060		Amino acid sequence of γ heavy chain variable region of LC.060 (Seq ID No: 19 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSL ISGSGGLTKYADSVKGRFTISRDNSKRTLYLQMNSLRAEDTAVYYCAKDIL VTGALDYWGQGTLVTVSS

230	γ heavy chain variable region of LC.063		Amino acid sequence of γ heavy chain variable region of LC.063 (Seq ID No: 20 in WO2006/029879)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVS IISGSGGFTYYADSVKGRFTISRDNSKKTLYLQMSRLRAEDTAIYFCAKDD IPAAGTFDPWGQGTLVTVSS
231	8E12 light chain variable region		Amino acid sequence of 8E12 light chain variable region (Seq ID No: 13 in US7,812,133)	DILMTQTPLSLPVSLGDQASISCRSSQSIVHGNGNTYLEWHLQKPGQSPK LLIYRVSNRFSGVPDRFSGSGSGTDFTLKINRVEAEDLGVYYCFQGSHVPY TFGGGTKVEIKR
232	8E12 heavy chain variable region		Amino acid sequence of 8E12 heavy chain variable region (Seq ID No: 14 in US7,812,133)	DIVMTQTPLSLPVSLGDQASMYCRSSQSPVHSNGNTYLHWYLQKPGQSP KLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHIP WTFGGGTKVEIKR
233	13G5 light chain variable region		Amino acid sequence of 13G5 light chain variable region (Seq ID No: 15 in US7,812,133)	QVQLQQPGAELVRPGASVkLSCKASGYTFTSYWLNWVKQRPGQGLEWIV MIDPSDSETHYNQVFKDKATLTVDKSSSTAYMQLSSLTSEDSAVYYCIRG RGNFYGGSHAMEYWGQGTLLTVSS
234	13G5 heavy chain variable region		Amino acid sequence of 13G5 heavy chain variable region (Seq ID No: 16 in US7,812,133)	QVQLQQPGAELVKPGTSVKLSCKASGYSFTSYWMHGVRQRPGQGLEWI GEIDPSNGRTNYNEKFKSKATLTVDKSSSTAYIQLSSLTSEDSAVYYCTRE RSPRYFDVWGAGTTLTVSS
235			HCDR3 motif	VRGXYYY

IMGT indicates that CDR is determined using IMGT nomenclature;

KABAT indicates that CDR is determined using Kabat nomenclature.

The numbering in the sequence correlation table takes precedence over any inconsistent numbering elsewhere in this text

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CLAIMS

1. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection.

2. A method according to claim 1, wherein the antibody or fragment thereof is administered via subcutaneous injection.

3. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or fragment thereof.

4. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug.

5. The method of claim 4 wherein after administering the disease modifying drug, the subject achieves an IGA-AD score of 0 or 1 for at least six months.

6. A method of treating Atopic Dermatitis in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, optionally according to any one of claims 1 to 5, wherein the antibody or fragment thereof is administered at least twice with at least one interval of 2 to 6 months.

7. The method of claim 6 wherein the antibody or fragment thereof is administered at least twice with at least one interval of around 3 months.

8. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered via subcutaneous injection.

9. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks during induction phase and once every 12 weeks during maintenance phase.

10. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks during induction phase and once every 12 weeks during maintenance phase, via subcutaneous injection.

11. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is a disease modifying drug.

12. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease or an inflammatory skin disorder in a human subject comprising administering a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof, wherein the antibody or fragment thereof is administered once every 4 weeks or once every 12 weeks or once every 6 months.

13. A method according to any preceding claim wherein each dose is of from 20 mg to 1000 mg.

14. A method according to any preceding claim wherein each dose is 62.5 mg, 125 mg, 150 mg, 250 mg or 500 mg.

15. A method according to any preceding claim wherein the dose is 125 mg.

16. A method according to any one of claims 1 to 14, wherein the dose is 150 mg.

17. A method according to any one of claims 1 to 14, wherein the dose is 62.5 mg.

18. A method according to any one of claims 1 to 14, wherein the dose is 250 mg.

19. A method according to any one of claims 1 to 14, wherein the dose is from 0.7 mg/kg to 6 mg/kg.

20. A method according to any one of claims 1-14, wherein the dose is from 1.4 mg/kg to 3 mg/kg.

21. The method of any preceding claim wherein the minimum blood serum concentration reached by the antibody or fragment thereof between any two injections (C_{min})is at least 2.5 µg/ml, 2.6 µg/ml, at

least 2.7 µg/ml, at least 2.8 µg/ml, at least 2.9 µg/ml, at least 3 µg/ml, at least 3.1 µg/ml, at least 3.2 µg/ml, at least 3.3 µg/ml, at least 3.4 µg/ml, at least 3.5 µg/ml, at least 3.6 µg/ml, at least 3.7 µg/ml, at least 3.8 µg/ml, at least 3.9 µg/ml, at least 4 µg/ml, at least 4.1 µg/ml, at least 4.2 µg/ml, at least 4.3 µg/ml, at least 4.4 µg/ml, at least 4.5 µg/ml, at least 4.6 µg/ml, at least 4.7 µg/ml, at least 4.8 µg/ml, at least 4.9 µg/ml, at least 5 µg/ml, at least 5.1 µg/ml, at least 5.2 µg/ml, at least 5.3 µg/ml, at least 5.4 µg/ml, at least 5.5 µg/ml, at least 5.6 µg/ml, at least 5.7 µg/ml, at least 5.8 µg/ml, at least 5.9 µg/ml, at least 6 µg/ml, at least 6.5 µg/ml, at least 7 µg/ml, at least 7.5 µg/ml, at least 8 µg/ml, at least 8.5 µg/ml, at least 9 µg/ml, at least 9.5 µg/ml, at least 10 µg/ml, at least 11 µg/ml, at least 12 µg/ml, at least 13 µg/ml, at least 14 µg/ml, at least 15 µg/ml, at least 16 µg/ml, at least 17 µg/ml, at least 18 µg/ml, at least 19 µg/ml, at least 20 µg/ml, at least 25 µg/ml, at least 30 µg/ml, at least 35 µg/ml, at least 40 µg/ml, at least 50 µg/ml, at least 60 µg/ml, at least 70 µg/ml, at least 80 µg/ml, at least 90 µg/ml, or at least 100 µg/ml.

22. The method of any preceding claim wherein the maximum blood serum concentration reached by the antibody or fragment thereof after administration of an injection and prior to administration of a subsequent injection (C_{max}) is at least about 1.5 µg / ml, at least about 2 µg / ml, at least about 5 µg / ml, at least about 10 µg / ml, at least about 20 µg / ml, at least about 30 µg / ml, at least about 40 µg / ml, at least about 50 µg / ml, at least about 60 µg / ml, at least about 70 µg / ml, at least about 80 µg / ml, at least about 90 µg / ml, at least about 100 µg / ml, at least about 150 µg / ml, at least about 200 µg / ml, at least about 300 µg / ml or at least about 550 µg / ml.

23. The method of any preceding claim wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 4 µg/mL to about 15 µg/mL.

24. The method of any preceding claim wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 20 µg/mL to about 45 µg/mL.

25. The method of any preceding claim wherein blood serum concentrations of the antibody or fragment thereof during treatment range between about 5 µg/mL to about 23 µg/mL.

26. The method of any preceding claim wherein blood serum concentrations of the antibody or fragment thereof during treatment are around or below 10 µg/mL.

27. The method of any preceding claim wherein the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC_{0-inf}]) injection may be from around 100,000 ng/ml*day to around 4,500,000 ng/ml*day or around 1,000,000 ng/ml*day to around 3,800,000 ng/ml*day.

28. The method of any preceding claim, comprising an induction phase and a maintenance phase.

29. The method of claim 28 wherein the induction dose is about 500 mg, 250 mg, about 125 mg or about 62.5 mg.

30. The method of claim 28 or 29 wherein the maintenance dose is about 500 mg, 250 mg, about 125 mg or about 62.5 mg.

31. The method of any one of claims 28 to 30, wherein the interval between two or more induction phase injections is about 4 weeks and the interval between two or more maintenance phase injections is about 12 weeks.

32. The method of any preceding claim wherein the administration is subcutaneous.

33. The method of claim 32 wherein the induction phase comprises administering at least five induction phase injections, wherein the first induction phase injection is a loading dose of 500 mg of the antibody or fragment thereof, followed by at least four subsequent induction phase injections, wherein each subsequent induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

34. The method of any one of claims 32 or 33 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 250 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

35. The method of claim 32 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 250 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

36. The method of claim 32 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 125 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

37. The method of any one of claims 32 or 36 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 125 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second

maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

38. The method of claim 32 wherein the induction phase comprises administering at least five induction phase injections, wherein each induction phase injection is a dose of 62.5 mg of the antibody or fragment thereof and wherein a second induction phase injection and each subsequent induction phase injection is administered 4 weeks after the preceding induction phase injection.

39. The method of any one of claims 32 or 38 wherein the maintenance phase comprises administering at least 3 maintenance phase injections, wherein each maintenance phase injection is a dose of 62.5 mg of the antibody or fragment thereof, wherein a first maintenance phase injection is administered at least 4 weeks after the final induction phase injection and wherein a second maintenance phase injection and each subsequent maintenance phase injection is administered at least 4 weeks after the preceding maintenance phase injection.

40. The method of any one of claims 32 to 39 wherein the first maintenance phase injection is administered 12 weeks after the final induction phase injection.

41. The method of any one of claims 32 to 40 wherein the second maintenance phase injection and each subsequent maintenance phase injection is administered 12 weeks after the preceding maintenance phase injection.

42. The method of any preceding claim wherein the antibody or fragment thereof is capable of exhibiting one or more pharmacokinetic properties selected from the group consisting of:

(a) a rate of clearance (CL) of about 0.05 to about 0.18 L/day;

(b) an absorption constant (ka) of about 0.11 to about 0.33 L/day;

(c) a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L;

(d) a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L;

(e) a rate of clearance from the central compartment to the second compartment (Q) of about 0.31 to about 0.93 L/day; and

(f) a bioavailability (Fabs1) of about about 0.6 to about 1.0.

43. The method of any preceding claim, wherein the subject is at least 18 years of age and/or less than 75 years of age.

44. The method of any preceding claim, wherein the atopic dermatitis is moderate-to-severe Atopic Dermatitis.

45. The method according to claim 44, wherein the subject is a patient candidate for systemic therapy.

46. The method according to claim 44, wherein the subject is a patient whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

47. The method of any preceding claim, wherein the atopic dermatitis is resistant, non responsive or inadequately responsive to treatment by either topical corticosteroids and/or systemic therapies or when those therapies are not advisable or wherein the subject has had an inadequate response to, was intolerant to, or is refractory to one or more topical corticosteroids.

48. A method according to any preceding claim further comprising administering a therapeutically effective amount of one or more topical corticosteroid.

49. The method of any one of claims 47 to 48 wherein the topical corticosteroid is selected from the group consisting of betamethasone dipropionate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate, mometasone furoate, diflorasone diacetate, halobetasol propionate, amcinonide, augmented betamethasone dipropionate, fluocinonide, halcinonide, triamcinolone acetonide, betamethasone valerate, clocortolone pivalate, desoximetasone, fluocinolone acetonide, flurandrenolide, fluticasone propionate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone valerate, prednicarbate, alclometasone dipropionate, desonide, hydrocortisone and hydrocortisone acetate.

50. The method of any one of claims 47 to 49 wherein the topical corticosteroid is selected from the group consisting of betamethasone dipropionate, betamethasone dipropionate;gentamicin sulphate, clobetasol propionate, dexamethasone, methylprednisolone, methylprednisolone aceponate and mometasone furoate.

51. A method of treating Atopic Dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in at least one improvement selected from the group consisting of:

a. a decrease from baseline in vIGA score of at least 2 points, or
b. achieving clear or almost clear skin (vIGA0/1) from baseline.

52. A method of treating Atopic Dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in at least one improvement selected from the group consisting of:

a. a decrease from baseline in EASI score of at least 50%, or

b. a decrease from baseline in EASI score of at least 75%, or
c. achieving EASI-75, or
d. achieving EASI-90, or
e. achieve at least 3 points a pruritus NRS, or
f. achieve at least 4 points a pruritus NRS, or
g. a decrease from baseline in SCORAD Index of at least 50%, or
h. a decrease from baseline in SCORAD Index of at least 55%, or
i. a decrease from baseline in affected BSA of at least 60%
j. a decrease from baseline in affected BSA of at least 70%

53. A method of treating an inflammatory disease, an inflammatory disorder, an immune-mediated disease, an immune-mediated disorder, an inflammatory skin disease, an inflammatory skin disorder, atopic dermatitis or moderate-to-severe atopic dermatitis in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody, or antigen-binding fragment thereof to the patient, wherein the administration of the anti-OX40L antibody, or antigen-binding fragment thereof results in the decrease in serum levels of at least one biomarker selected from the group consisting of: IL-13, IL-22, IL-17A, IL-31 and IgE.

54. The method of any preceding claim, wherein the at least one of the decrease in serum levels of at least one biomarker selected from the group consisting of: IL-13, IL-22, IL-17A, IL-31 and IgE is maintained for at least 12 weeks or at least 24 weeks following the final dose and/or wherein at least one of the improvements is maintained for at least 12 weeks or at least 24 weeks following the final dose.

55. The method of any preceding claim, wherein the atopic dermatitis has been assessed by determining a baseline EASI score.

56. The method of any preceding claim wherein the post-administration EASI score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

57. The method of any preceding claim wherein the post-administration EASI and/or further post-administration EASI is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

58. The method of any preceding claim wherein the post-administration EASI and/or further post-administration EASI is determined at least around 169 days after administering a first injection of the

antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

59. The method of any preceding claim wherein the post-administration EASI and/or further post-administration EASI is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration EASI and/or further post-administration EASI is EASI50, EASI75, EASI90 or EASI100.

60. The method of any preceding claim wherein the Atopic Dermatitis is treated as evidenced by a reduction in the EASI score by at least 40% after the third injection as a treatment dose and wherein the reduction in EASI score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

61. The method of any preceding claim, wherein the atopic dermatitis has been assessed by determining a baseline vIGA-AD score.

62. The method of any preceding claim wherein the post-administration vIGA-AD score is 0 or 1.

63. The method of any preceding claim wherein the post-administration vIGA-AD score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

64. The method of any preceding claim wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 113 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

65. The method of any preceding claim wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 169 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

66. The method of any preceding claim wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is determined at least around 253 days after administering a first injection of the antibody or fragment thereof and wherein the post-administration vIGA-AD and/or further post-administration vIGA-AD is:

(a) A vIGA-AD score of 0 or 1, and/or

(b) reduced at least 2 points relative to the baseline vIGA-AD score.

67. The method of any preceding claim wherein the Atopic Dermatitis is treated as evidenced by a reduction in the vIGA-AD score by at least 2 points after the third injection as a treatment dose and wherein the reduction in vIGA-AD score is persistent for at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection as a treatment dose.

68. A therapeutic dosage form of a pharmaceutical composition comprising an anti-OX40L antibody, or antigen-binding fragment thereof, wherein administration of the dose form to a human provides one or more of:

(a) a serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection from around 100,000 ng/ml*day to around 4,500,000 ng/ml*day or around 1,000,000 ng/ml*day to around 3,800,000 ng/ml*day

(b) a rate of clearance (CL) of about 0.05 to about 0.18 L/day;

(b) an absorption constant (ka) of about 0.11 to about 0.33 L/day;

(c) a volume of central compartment volume (Vc) of about 1.6 to about 5.0 L;

(d) a second (peripheral compartment) volume (Vp1) of about 1.2 to about 3.6 L;

(e) a rate of clearance from the central compartment to the second compartment (Q) of about 0.31 to about 0.93 L/day; and

(f) a bioavailability (Fabs1) of about about 0.6 to about 1.0.

69. An anti-OX40L antibody, or antigen-binding fragment thereof, for use in a method of treating atopic dermatitis in accordance with any one of claims 1 to 67.

70. A glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit comprising an anti-OX40L antibody, or antigen-binding fragment thereof for use in a method of treating atopic dermatitis in accordance with any one of claims 1 to 67.

71. The use of an anti-OX40L antibody, or antigen-binding fragment thereof, for the manufacture of a medicament for the treatment of atopic dermatitis in accordance with any one of claims 1 to 67.

72. The use of a glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector or kit comprising an anti-OX40L antibody, or antigen-binding fragment thereof, for the

manufacture of a medicament for the treatment of Atopic Dermatitis in accordance with any one of claims 1 to 67.

73. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the HCDR3 of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46).

74. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the HCDR2 of antibody 2D10 (SEQ ID No:38 or SEQ ID No:44).

75. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the HCDR1 of antibody 2D10 (SEQ ID No:36 or SEQ ID No:42).

76. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the LCDR3 of antibody 2D10 (SEQ ID No:54 or SEQ ID No:60).

77. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the LCDR2 of antibody 2D10 (SEQ ID No:52 or SEQ ID No:58).

78. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the LCDR1 of antibody 2D10 (SEQ ID No:50 or SEQ ID No:56).

79. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises:
the CDRs of antibody 2D10 (SEQ ID No:40 or SEQ ID No:46 for CDRH3, SEQ ID No:38 or SEQ ID No:44 for CDRH2, SEQ ID No:36 or SEQ ID No:42 for CDRH1, SEQ ID No:50 or SEQ ID No:56 for CDRL1, SEQ ID No:52 or SEQ ID No:58 for CDRL2 and SEQ ID No:54 or SEQ ID No:60 for CDRL3).

80. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises the VH and/or VL domains selected from the following:
the VH and/or VL domains of antibody 2D10 (SEQ ID No:34 for VH and/or SEQ ID No:48 for VL).

81. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the antibody or fragment thereof comprises a heavy chain having an amino acid sequence according to SEQ ID No:62 and a light chain having an amino acid sequence according to SEQ ID No:64.

82. A method, glass vial, drug delivery device, prefilled syringe, microinfusor, pen delivery device, autoinjector, kit, or use according to any preceding claim, wherein the subject is classified as a Th2 AD patient and/or a non-Th2 AD patient.

83. A method of treating atopic dermatitis in a subject, the method comprising:

selecting a subject having atopic dermatitis; and

administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an anti-OX40L antibody or antigen-binding fragment thereof, wherein the anti-OX40L antibody or antigen-binding fragment thereof comprises heavy chain complementarity regions (HCDRs) of SEQ ID NOs: 42, 44 and 46, and light chain complementarity determining regions (LCDRs) of SEQ ID NOs: 56, 58 and 60.

84. The method of claim 83, wherein the administration of the anti-OX40L antibody or antigen-binding fragment thereof results in the decrease in serum levels in the subject of at least one biomarker selected from the group consisting of: IL-13, IL-22, IL-17A, IL-31 and IgE.

85. The method of claim 84, wherein the decrease in serum levels of at least one biomarker is maintained for at least 12 weeks or at least 24 weeks following the final dose.

86. The method of claim 83, wherein the atopic dermatitis has been assessed by determining a baseline EASI score.

87. The method of claim 86, wherein a post-administration EASI score is maintained, without additional administration of an anti-OX40L antibody, or antigen-binding fragment thereof, for:

(a) at least 2 months, at least 3 months, at least 4 months, at least 5 months or at least 6 months after administration of the last injection; or

(b) at least about 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 113, 169 or 253 days.

88. The method of claim 83, wherein the atopic dermatitis has been assessed by determining a baseline vIGA-AD score.

89. The method of claim 88, wherein the post-administration vIGA-AD score is 0 or 1.