

THERAPEUTIC ANTIBODY FORMULATIONS

The present invention is in the field of medicine. More particularly, the present invention relates to aqueous pharmaceutical formulations comprising therapeutic antibodies that are suitable for subcutaneous ("SC"), intramuscular ("IM"), and/or intraperitoneal ("IP") administration. Still more particularly, the present invention relates to pharmaceutical formulations of an anti-IL-23p19 antibody. These anti-IL-23p19 antibody pharmaceutical formulations are expected to be useful in treating at least psoriasis (Ps), psoriatic arthritis (PsA), ulcerative colitis (UC), Crohn's Disease (CD) and/or ankylosing spondylitis.

Pharmaceutical formulations of anti-IL-23p19 antibodies are needed for the treatment of patients with Ps, PsA UC, CD and/or ankylosing spondylitis. Administration of such therapeutic antibodies via SC, IP and/or IM administration is both common and advantageous. Such routes of administration allow the therapeutic antibody to be delivered in a short period of time and allow patients to self-administer therapeutic antibodies without visiting a medical practitioner. Certain concentrations of anti-IL-23p19 antibodies are needed for pharmaceutical formulations so that the antibody can be delivered SC, IP and/or IM to the patient. These pharmaceutical formulations with a certain concentration of the anti-IL-23p19 antibody must maintain physical and chemical stability of the anti-IL-23p19 antibody. However, formulating therapeutic antibodies into aqueous pharmaceutical formulations suitable for SC, IM and/or IP administration is both challenging and unpredictable.

The challenge and unpredictability associated with formulating therapeutic antibodies into aqueous pharmaceutical formulations suitable for SC, IM and/or IP administration is due, in part, to the numerous properties a pharmaceutical formulation must possess to be therapeutically viable. Pharmaceutical formulations must provide stability to the therapeutic antibody in solution while, at the same time, maintaining the therapeutic antibody's functional characteristics essential for therapeutic efficacy such as target affinity, selectivity and potency. In addition, the aqueous pharmaceutical formulation must also be safe for administration to, and well tolerated by, patients as well as being suitable for manufacturing and storage.

-2-

Formulating high concentrations of therapeutic antibodies is even more complex. For example, increased rates of antibody degradation, cleavage, clipping, high molecular weight aggregation, dimerization, trimerization, precipitation pH shift, turbidity, solution color change, changes in charge, isomerization, oxidation and/or deamination (all of which affect the therapeutic antibody concentration, functionality and efficacy) have been reported for formulations of highly concentrated therapeutic antibodies. Another known challenge when formulating high concentrations of therapeutic antibodies is an increase in viscosity which can negatively affect SC, IM and/or IP administration of a pharmaceutical formulation.

10 Mirikizumab, CAS Registry No. 1884201-71-1, is a humanized immunoglobulin (Ig) G4-variant monoclonal antibody targeting the p19 subunit of human IL-23 and is described in U.S. Patent No. 9,023,358. Mirikizumab is being evaluated for the treatment of patients with moderate to severe plaque psoriasis, UC and CD. Mirikizumab may be administered to patients subcutaneously in a highly concentrated (75 - 150 mg/mL) pharmaceutical formulation. It has been found in pre-formulation studies that mirikizumab is less stable in formulations at the lower and higher pH values (pH < 5.0 and pH > 7.0). Mirikizumab samples formulated at high concentrations exhibited more soluble aggregates relative to samples formulated at lower concentrations as determined by SEC. Moreover, certain formulations of mirikizumab at concentrations of at least 15 50 mg/mL showed significant protein cryo-precipitation. Pharmaceutical formulations for certain concentrations of anti-IL-23p19 antibodies are needed that avoid these observed problems. The pharmaceutical formulations provided herein satisfy the aforementioned needs. More particularly, the pharmaceutical formulations provided herein are suitable for SC, IM and/or IP administration of high concentrations of mirikizumab while 20 preserving the functional characteristics of mirikizumab essential for therapeutic efficacy.

Accordingly, there is provided a pharmaceutical formulation comprising:

- (i) 50 mg/mL - 150 mg/mL of a IL-23p19 antibody;
 - (ii) 8 mM - 12 mM of a citrate buffer;
 - (iii) 100 - 200 mM of sodium chloride (NaCl); and
 - 30 (iv) 0.01% w/v to 0.05% w/v of a surfactant,
- wherein the pH of the formulation is between 5.0 to 6.0,

-3-

and wherein the anti-IL-23p19 antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.

5 In an embodiment of the present invention, the anti-IL-23p19 antibody comprises a light chain (LC) and a heavy chain (HC), wherein the amino acid sequence of the LC is SEQ ID NO: 10 and the amino acid sequence of the heavy chain is SEQ ID NO: 9.

In a preferred embodiment of the present invention, the anti-IL-23p19 antibody is mirikizumab.

10 In an alternative embodiment of the present invention, the pharmaceutical formulation comprises an anti-IL-23p19 antibody wherein the anti-IL-23p19 antibody comprises a LCVR and a HCVR, wherein the LCVR comprises amino acid sequences LCDR1, LCDR2, and LCDR3, and the HCVR comprises amino acid sequences HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO:4, LCDR2 is SEQ ID NO:5, LCDR3 is SEQ ID NO:6, HCDR1 is SEQ ID NO:1, HCDR2 is SEQ ID NO:2, and
15 HCDR3 is SEQ ID NO:3.

In a further embodiment of the present invention, the concentration of the anti-IL-23p19 antibody is about 75 mg/mL to about 150 mg/mL. Preferably, the concentration of the anti-IL-23p19 antibody is about 100 mg/mL to about 150 mg/mL. Further preferably, the concentration of the anti-IL-23p19 antibody is about 100 mg/mL. Alternatively,
20 preferably, the concentration of the anti-IL-23p19 antibody is about 125 mg/mL.

In a still further embodiment of the present invention, the concentration of the citrate buffer is about 10 mM. Preferably, the citrate buffer is a sodium citrate buffer.

In a still further embodiment of the present invention, the surfactant is polysorbate 20 or polysorbate 80. Preferably, the surfactant is polysorbate 80. Further preferably, the
25 concentration of the surfactant is about 0.03% (w/v).

In a still further embodiment of the present invention, the concentration of NaCl is about 150 mM.

In a still further embodiment of the present invention the pH of the formulation is about 5.5.

30 In a preferred embodiment of the present invention, the formulation comprises:

- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
- (ii) 10 mM of sodium citrate buffer;

-4-

- (iii) 150 mM of NaCl; and
 - (iv) 0.03% w/v of polysorbate 80,
- wherein the pH of the formulation is about 5.5.

Preferably, the formulation comprises 100 mg/mL of mirikizumab.

5 Alternatively, preferably, the formulation comprises 125 mg/mL of mirikizumab.

In a further aspect of the present invention, there is also provided a method of treating and/or preventing psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis, wherein the method comprises administering to a patient a therapeutically effective amount of a pharmaceutical formulation of the present invention.

10 In a still further aspect of the present invention, there is provided a pharmaceutical formulation of the present invention for use in the treatment and/or prevention of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

In a still further aspect of the present invention, there is provided the use of a
15 pharmaceutical formulation of the present invention in the manufacture of a medicament for use in the treatment of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

In addition to the difficulties in formulating antibody therapeutics described above, undesirable injection-associated pain, even after a syringe needle is removed, has
20 been reported with such routes of administration and can impair patient compliance with therapy. Injection-associated pain has been reported with formulations having increased viscosity. Injection-associated pain of pharmaceutical formulations comprising therapeutic antibodies is a complex, multifactorial issue. For example, each individual component, and/or concentration, ratio and characteristic thereof, of an aqueous
25 pharmaceutical formulation can impact injection-associated pain associated with a therapeutic. Likewise, individual components (and/or concentrations, ratios and characteristics thereof) can impact the stability, functional characteristics, manufacturability and/or tolerability of a formulated therapeutic antibody in an aqueous pharmaceutical formulation. Thus, while a specific formulation adjustment may provide
30 a beneficial impact to a given aspect of the formulation, the same adjustment may also negatively impact other aspects of the formulation. Even further adding to the complexity, a nearly limitless number of different formulation components (e.g., buffers

-5-

and excipients), as well as concentrations and ratios thereof, have been reported. However, there remains little-to-no correlation for predicting the impact of a specific formulation on the various properties and characteristics of a given therapeutic antibody.

Accordingly, there is also a need for a pharmaceutical formulation of therapeutic antibodies suitable for SC, IM and/or IP administration and which is well tolerated by patients, exhibiting a therapeutically beneficial level of injection-associated pain. Even more particularly, there is a need for a pharmaceutical formulation of mirikizumab suitable for SC, IM and/or IP administration and which is well tolerated by patients, exhibiting an improved level of injection-associated pain over alternative formulations of mirikizumab. Such pharmaceutical formulation must also provide stability for the therapeutic antibody and preserve the properties of the therapeutic antibody essential for therapeutic efficacy. Such pharmaceutical formulations must also be amenable to manufacturing, preferably having an extended shelf life. Such pharmaceutical formulations must also be suitable for SC, IM and/or IP administration *via* a pre-filled syringe or an autoinjector.

The pharmaceutical formulations provided herein satisfy the aforementioned needs. More particularly, the pharmaceutical formulations provided herein are suitable for SC, IM and/or IP administration of high concentrations of mirikizumab (for example, appropriate viscosity) while preserving the functional characteristics of mirikizumab essential for therapeutic efficacy. The pharmaceutical formulations provided herein are also well tolerated by patients, and may exhibit an improved level of injection-associated pain over alternative pharmaceutical formulations of mirikizumab and providing a therapeutically favorable level of injection-associated pain.

Accordingly, there is provided a pharmaceutical formulation comprising:

- (i) 50 mg/mL – 150 mg/mL of an IL-23p19 antibody;
 - (ii) 3 mM – 12 mM of a histidine buffer;
 - (iii) 25 - 75 mM of NaCl;
 - (iv) 2-5% w/v of a tonicity agent; and
 - (iv) 0.01% w/v to 0.05% w/v of a surfactant,
- wherein the pH of the formulation is between 5.0 to 6.0,

-6-

and wherein the anti-IL-23p19 antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.

5 In an embodiment of the present invention, the anti-IL-23p19 antibody comprises a light chain (LC) and a heavy chain (HC), wherein the amino acid sequence of the LC is SEQ ID NO: 10 and the amino acid sequence of the heavy chain is SEQ ID NO: 9.

In a preferred embodiment of the present invention, the anti-IL-23p19 antibody is mirikizumab.

10 In an alternative embodiment of the present invention, the pharmaceutical formulation comprises an anti-IL-23p19 antibody wherein the anti-IL-23p19 antibody comprises a LCVR and a HCVR, wherein the LCVR comprises amino acid sequences LCDR1, LCDR2, and LCDR3, and the HCVR comprises amino acid sequences HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO:4, LCDR2 is SEQ ID NO:5, LCDR3 is SEQ ID NO:6, HCDR1 is SEQ ID NO:1, HCDR2 is SEQ ID NO:2, and
15 HCDR3 is SEQ ID NO:3.

In a further embodiment of the present invention, the concentration of the anti-IL-23p19 antibody is about 75 mg/mL to about 150 mg/mL. Preferably, the concentration of the anti-IL-23p19 antibody is about 100 mg/mL to about 150 mg/mL. Further preferably, the concentration of the anti-IL-23p19 antibody is about 100 mg/mL. Alternatively,
20 preferably, the concentration of the anti-IL-23p19 antibody is about 125 mg/mL.

In a still further embodiment of the present invention, the concentration of the histidine buffer is about 5 mM.

In a still further embodiment of the present invention, the tonicity agent is mannitol.

25 Preferably, the concentration of mannitol is 3.3% w/v.

In a still further embodiment of the present invention, the surfactant is polysorbate 20 or polysorbate 80.

Preferably, the surfactant is polysorbate 80.

Further preferably, the concentration of the surfactant is about 0.03% (w/v).

30 In a still further embodiment of the present invention, the concentration of NaCl is about 50 mM.

-7-

In a still further embodiment of the present invention, the pH of the formulation is about 5.5.

In a preferred embodiment of the present invention, the formulation comprises:

- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
- 5 (ii) 5mM of a histidine buffer;
- (iii) 50 mM of NaCl;
- (iv) 3.3% w/v of mannitol; and
- (v) 0.03% w/v of polysorbate 80,

wherein the pH of the formulation is 5.5.

10 Preferably, the formulation comprises 100 mg/mL of mirikizumab. Alternatively, preferably, the formulation comprises 125 mg/mL of mirikizumab.

In a further aspect of the present invention, there is provided a method of treating and/or preventing psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis, wherein the method comprises administering to a patient a
15 therapeutically effective amount of a pharmaceutical formulation of the present invention.

In a still further aspect of the present invention, there is provided a pharmaceutical formulation of the present invention for use in the treatment and/or prevention of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

20 In a still further aspect of the present invention, there is provided the use of a pharmaceutical formulation of the present invention in the manufacture of a medicament for use in the treatment of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

In a still further aspect of the present invention, there is provided a method of
25 reducing injection-associated pain experienced by a patient at the time of, or shortly after, SC, IP and/or IM administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering to a patient a pharmaceutical formulation of the present invention, wherein, said step of administering provides a therapeutically favorable level of injection-associated pain.

30 Preferably, the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

-8-

In a still further aspect of the present invention, there is provided an improved method for SC administration of an anti-IL-23p19 antibody to a patient in need thereof, wherein the improvement comprises a reduction in injection-associated pain upon SC administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical formulation of the present invention, wherein said step of administering provides an improved level of injection-associated pain and/or provides a therapeutically favorable level of injection-associated pain. Preferably, the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

In a still further aspect of the present invention, there is provided an improved method of treating at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis, wherein the improvement comprises a reduction in injection-associated pain upon the SC administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical formulation as described herein, wherein said step of administering provides an improved level of injection-associated pain and/or provides a therapeutically favorable level of injection-associated pain. Preferably, the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

As used herein, the expression "pharmaceutical formulation" means a solution having at least one therapeutic antibody capable of exerting a biological effect in a human, at least one inactive ingredient (e.g., buffer, excipient, surfactant, etc.) which, when combined with the therapeutic antibody, is suitable for therapeutic administration to a human. Pharmaceutical formulations of the present disclosure are stable formulations wherein the degree of degradation, modification, aggregation, loss of biological activity and the like, of therapeutic antibodies therein, is acceptably controlled and does not increase unacceptably with time.

As used herein, the term "antibody" refers to an immunoglobulin G (IgG) molecule comprising two heavy chains ("HC") and two light chains ("LC") interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region ("HCVR") and a heavy chain constant region ("CH"). Each light chain is comprised of a light chain variable region ("LCVR") and a light chain constant region

(“CL”). Each HCVR and LCVR are further sub-dividable into regions of hypervariability, termed complementarity determining regions (“CDR”), interspersed with regions that are more conserved, termed framework regions (“FR”). Each HCVR and LCVR is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of each HC and LC contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

As used interchangeably herein “an antibody that binds to the p19 subunit of human IL-23” or “an anti-IL-23p19 antibody” refers to an antibody that binds to the p19 subunit of human IL-23 but does not bind to the p40 subunit of human IL-23. Examples of such antibodies include mirikizumab, guselkumab, tildrakizumab and risankizumab.

Guselkumab, CAS Registry No. 1350289-85-8, is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of human IL-23 that has been approved for the treatment of plaque psoriasis. The antibody and methods of making same are described in US Patent No. 7,935,344.

Tildrakizumab, CAS Registry No. 1326244-10-3, is a humanized, IgG1 kappa monoclonal antibody targeting the p19 subunit of human IL-23 that has approved for the treatment of moderate to severe plaque psoriasis. The antibody and methods of making same are described in US Patent No. 8,293,883.

Risankizumab, CAS Registry No. 1612838-76-2, is a humanized, IgG1 kappa monoclonal antibody targeting the p19 subunit of human IL-23. The antibody and methods of making same are described in US Patent No. 8,778,346. Risankizumab is has been approved for the treatment moderate to severe plaque psoriasis.

Brazikumab, CAS Registry No. 1610353-18-8, is a humanized, IgG2-lambda monoclonal antibody targeting the p19 subunit of human IL-23. The antibody and methods of making same are described in US Patent No. 8,722,033. Brazikumab is being evaluated for the treatment CD and UC.

As may be used herein, the terms “about” or “approximately”, when used in reference to a particular recited numerical value or range of values, means that the value may vary from the recited value by no more than 10% (e.g., +/- 10%). For example, as

-10-

used herein, the expression "about 100" includes 90 and 110 and all values in between (e.g., 91, 92, 93, 94, etc.).

As used herein, the phrase "injection site pain" refers to pain attributable to injection of a liquid formulation subcutaneously and localized to the site of the injection.

- 5 Pain may be evaluated using any type of pain assessment known in the art, including, for example, visual analog scales (VAS), qualitative assessments of pain, or needle pain assessments. For example, subject-perceived injection site pain may be assessed using the Pain Visual Analog Scale (VAS). A VAS is a measurement instrument that measures pain as it ranges across a continuum of values, e.g., from none to an extreme amount of pain.
- 10 Operationally, a VAS is a horizontal line, about 100 mm in length, anchored by numerical and/or word descriptors, e.g., 0 or 10, or "no pain" or "excruciating pain," optionally with additional word or numeric descriptors between the extremes, e.g., mild, moderate, and severe; or 1 through 9) (see, e.g., Lee J S, et al. (2000) AcadEmerg Med 7:550, or Singer and Thods (1998) Academic Emergency Medicine, 5:1007). Pain may be assessed at a
- 15 single time or at various times following administration of a formulation such as, for example, immediately after injection, at about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 45 minutes after injection. Severity of pain may be categorized, according to the VAS tool, as mild pain (≤ 30 mm); moderate pain (>30 mm - ≤ 70 mm) and severe pain (>70 mm). A desired property of a stable pharmaceutical formulation is being well
- 20 tolerated by patients, for example, providing a therapeutically favorable level of injection-associated pain (e.g., a VAS score of <30 mm and/or <20 mm). As is known, the components, and concentrations and/or ratios thereof, of a pharmaceutical formulation may impact injection-associated pain experienced by the patient.

- As used interchangeably herein, "treatment" and/or "treating" and/or "treat" are
- 25 intended to refer to all processes wherein there may be a total elimination, slowing or delaying, reduction in severity or frequency (e.g., of flares or episodes), interruption or stopping of the progression of disease and/or symptoms thereof, but does not require a total elimination of all disease symptoms. Treatment includes administration of an aqueous pharmaceutical formulation of the present disclosure for treatment of a disease in
- 30 a human that would benefit from at least one of the above-listed processes, including: (a) inhibiting further progression of disease symptoms and effects, i.e., arresting its development; (b) relieving the disease, i.e., causing an elimination or regression of

-11-

disease, disease symptoms or complications thereof; and (c) preventing or reducing the frequency of disease episodes or flares. According to specific embodiments, the pharmaceutical formulations provided herein may be used in the treatment of at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing
5 spondylitis.

As used interchangeably herein, the term "patient," "subject" and "individual," refers to a human. Unless otherwise noted, the subject is further characterized as having, being at risk of developing, or experiencing symptoms of a disease that would benefit from administration of a pharmaceutical formulation disclosed herein.

10 As used interchangeably herein, an "effective amount" or "therapeutically effective amount" of a pharmaceutical formulation of the instant disclosure refers to an amount necessary (at dosages, frequency of administration and for periods of time for a particular means of administration) to achieve the desired therapeutic result. An effective amount of pharmaceutical formulation of the present disclosure may vary according to
15 factors such as the disease state, age, sex, and weight of the subject and the ability of the pharmaceutical formulation of the present disclosure to elicit a desired response in the subject. An effective amount is also one in which any toxic or detrimental effects of the pharmaceutical formulation of the present disclosure are outweighed by the therapeutically beneficial effects.

20 The pharmaceutical formulations of the present invention may be administered to a patient via parenteral administration. Parenteral administration, as understood in the medical field, refers to the injection of a dose into the body by a sterile syringe or some other drug delivery system including an autoinjector or an infusion pump. Exemplary drug delivery systems for use with the pharmaceutical formulations of the present
25 disclosure are described in the following references, the disclosures of which are expressly incorporated herein by reference in their entirety: U.S. Patent Publication No. 2014/0054883 to Lanigan et al., filed March 7, 2013 and entitled "Infusion Pump Assembly"; U.S. Patent No. 7,291,132 to DeRuntz et al., filed February 3, 2006 and entitled "Medication Dispensing Apparatus with Triple Screw Threads for Mechanical
30 Advantage"; U.S. Patent No. 7,517,334 to Jacobs et al., filed September 18, 2006 and entitled "Medication Dispensing Apparatus with Spring-Driven Locking Feature Enabled by Administration of Final Dose"; and U.S. Patent No. 8,734,394 to Adams et al., filed

-12-

August 24, 2012 and entitled “Automatic Injection Device with Delay Mechanism Including Dual Functioning Biasing Member.” Parenteral routes include IM, SC and IP routes of administration.

BRIEF DESCRIPTION OF FIGURES

Figure 1 is a contour plot of mirikizumab concentration vs. pH that shows the relationship of target pH to antibody concentration on predicted monomer purity.

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Figure 2 illustrates the glide force data for Formulations 1 and 21-29.

EXAMPLES

10 **Example 1: Production of Antibodies**

Anti-IL-23p19 antibodies can be made and purified as follows. An appropriate host cell, such as CHO, is either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both LC and both HC, such as each LC being SEQ ID NO: 10 and each HC being SEQ ID NO: 9. Clarified media, into which the antibody has been secreted, is purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a Protein A or G Sepharose FF column that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient. Antibody fractions are detected, such as by SDS-PAGE, and then are pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 99%. The product may be immediately frozen at -70°C in the formulation matrix of the invention or may be lyophilized. The amino acid and nucleic acid sequences for the exemplified antibody are provided below.

30

Example 2: Formulation Study A**Study design and preparation of anti-IL-23p19 antibody pharmaceutical formulations**

The study design assessed the impact of four factors: concentration of anti-IL-23p19 antibody (mirikizumab), concentration of sodium chloride, concentration of polysorbate 80 and pH. The formulations assessed are shown in **Table 1**.

Formulation	pH	Antibody Conc. (mg/mL)	Ps-80 (% w/v)	NaCl (mM)	Container
1	5.5	85	0.03	150	PFS (1 mL)
2	5.5	20	0.01	100	PFS (1 mL)
3	5.0	20	0.01	200	PFS (1 mL)
4	6.0	150	0.05	100	PFS (1 mL)
5	6.0	20	0.05	200	PFS (1 mL)
6	6.0	85	0.01	200	PFS (1 mL)
7	6.0	150	0.01	150	PFS (1 mL)
8	5.0	20	0.05	150	PFS (1 mL)
9	5.0	85	0.05	100	PFS (1 mL)
10	5.5	150	0.05	200	PFS (1 mL)
11	5.0	150	0.03	200	PFS (1 mL)
12	6.0	20	0.03	100	PFS (1 mL)
13	5.0	150	0.01	100	PFS (1 mL)
14	5.5	85	0.03	150	PFS (1 mL)
15	5.5	100	0.03	150	PFS (1 mL)
16	5.5	125	0.03	150	PFS (1 mL)
17	5.5	50	0.05	150	Vial
18	5.5	20	0.01	150	Vial
19	5.5	20	0.05	150	Vial
20	5.5	125	0.03	150	PFS (2 mL)

Table 1: Study design

-15-

The antibody concentration was examined in Formulations 1-20 at 20, 85, 100, 125 and 150 mg/mL. The wide antibody concentration was chosen to account for multiple possible presentations for mirikizumab drug product and based on pre-formulation data which provided clear correlations between some forms of degradation (such as aggregation) and concentration. Polysorbate 80 was studied at three concentrations (0.01, 0.03 and 0.05% w/v). NaCl effects were explored at the concentrations 100, 150 and 200 mM. pH effects were studied over 5.0 to 6.0 as pre-formulation studies and biophysical screening indicated that the regional of optimal global stability was pH 5.5 to 6.0.

Based on pre-formulation data, no significant effects on stability were observed from various container closure types. Therefore, a 1 mL prefilled syringe (PFS) was used to cover the study design for consistency. Vials were used for Formulations 17-19. Formulation 20 (with a 2 mL PFS) was included as a direct comparison with Formulation 16 to determine if there may be a significant contribution from different syringes.

Formulations 1-20 were independently prepared in the order specified. The material for each formulation was prepared by dialyzing drug substance into the specified formulation condition. Dialyzed solution was then spiked with an appropriate amount of polysorbate and diluted to the prescribed antibody concentration with formulation buffer. Samples were filtered with 0.22 µm filters and aseptically filled into the designated container closure systems.

The buffer excipient composition consists of citric acid anhydrous (QD514N, Lot No. C490136), sodium citrate dihydrate (QD517A, Lot No. C487212), sodium chloride (QD515R, Lot No. C481616), polysorbate 80 (QD513DVIE, Lot No. C457300).

The anti-IL-23p19 antibody is mirikizumab, which comprises a LC of SEQ ID NO: 10, and a HC of SEQ ID NO: 9 (Demo Lot No. EL01685-039-F-Fill).

Analytical and characterization techniques selected to measure the chemical and physical stability and properties of the formulations included size exclusion chromatography (SEC) HPLC, imaged capillary isoelectric focusing iCIEF, reduced and non-reduced CESDS, HIAC, microflow imaging (MFI), visual appearance, pH (USP <921>), UV absorbance to measure protein concentration syringe functionality and device testing.

-16-

Samples were stored at four temperature conditions (5°C, 15°C, 25°C and 35°C) with the syringe stored horizontally and vials inverted. This range of temperatures enables estimations of the activation energies of each analytical response variable assuming Arrhenius kinetics. In addition, higher temperature storage enabled earlier prediction of optimal formulation conditions to speed the drug product development process.

The sampling schedule for Formulations 1-14 is outlined in **Table 2**. The schedule is designed to capture four time points for 25°C and 35 °C at three months and three time points for other storage conditions. This sampling frequency permits sufficient information to fit the data in prediction models. After the three-month time point, activation energies (Ea) were calculated employing an Arrhenius kinetic model to correlate results at accelerated temperatures with predicted 5°C stability. An Ea value of 21.5 kcal/mol was used to fit the SEC (monomer, polymer and post-monomer), iCIEF (main peak, total acidic and total basic variants), and non-reduced and reduced CE-SDS. This fit is based in part upon what has been observed with other IgG4 antibodies. The time points denoted by X are conditions where samples were analyzed by SEC, iCIEF, reduced and non-reduced CE-SDS, pH, UV content and visual appearance. Testing by HIAC and MFI was performed less frequently.

Temp (°C)	Initial	Weeks	Months			
		2	1	2	3	6
5	X ^{a, b, c}			X	X ^{a, b}	X ^{a, b}
15				X	X ^b	
25			X ^b	X	X ^{a, b}	X ^{a, b}
35			X ^b	X	X ^{a, b}	

X = sample time point, a = HIAC sample, b = MFI sample.

Table 2: Sampling schedule for Formulations 1-14

The sampling schedule for Formulations 15-20 is shown in **Table 3**. Formulations 15-20 represent formulations may be assessed in clinical trials in human patients. These formulations were put in relevant container closure systems (which included vials and the

2.25mL syringes). These formulations were assessed to confirm stability of these potential drug products and to understand if there were any effects of container closure type on stability.

		Weeks	Months						
Temp (°C)	Initial	2	1	2	3	6	9	12	18
5	X ^{a, b, c}				X ^{a, b}	X ^b	X	X ^{a, b}	X ^b
15									
25			X ^b		X ^{a, b}	X			
35		X	X ^b	X	X ^{a, b}				

5 X = sample time point, a = HIAC sample, b = MFI sample.

Table 3: Sampling schedule for Formulations 15-20

Formulation Study A - Results - Size Exclusion Chromatography

10 SEC percent monomer values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 4a-4d**. The 35°C data are displayed through three months. The 25°C data are displayed through 6 months, and 5°C data are shown up to 18 months (only for Formulations 15 and 20). Increasing temperature resulted in decreases in percent monomer. The largest changes in this data set are < 2%. Percent monomer is remains above 98.6% for samples tested at 5°C through 18 months except for one result at 9 months.

15 Monomer and polymer values (not shown) inversely mirror each other closely and degradation observed by SEC was primarily the result of soluble aggregate (polymer) formation.

20 Predicted effects of each input variable on SEC monomer purity over 24-months at 5°C are modelled using results obtained from data up to 3 months. All four temperatures were used to model the modified Arrhenius kinetics. An activation energy (Ea) of 21.5 kcal/mol was used to generate these predictions. Predictions of percent monomer in all cases are > 98% and the largest predicted change is > 1.3% indicating that mirikizumab is stable over the entire design region. This is in close agreement with the empirical data shown in **Tables 4a-4d**. Increased mirikizumab concentration through the

-18-

range studied resulted in greater monomer loss. This relationship is likely a function of the increased probability of intermolecular interactions between antibodies. Slightly increased stability was observed at lower pH conditions in the study consistent with preformation studies. Polysorbate 80 concentration, NaCl concentration and container closure appear to have no significant effect. For the two factors that had an effect (antibody concentration, pH) the difference between the best and worst locations in the design region was <1.0%.

Figure 1 is a contour plot that shows the relationship of target pH to antibody concentration on predicted monomer purity. The Prob > F Effect Test value for pH Target*Concentration Target is 0.0130 indicating that interaction is statistically significant. The pH effect on purity is stronger at higher antibody concentration.

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	99.0355	98.8508	98.8962	98.9358			
2	99.2563	99.2886	99.3144	99.2253			
3	99.3694	99.3511	99.4345	99.3993			
4	98.6003	98.5643	98.5050	98.4485			
5	99.1434	99.1082	99.0041	99.0904			
6	98.7584	98.7591	98.7379	98.6326			
7	98.6183	98.2753	98.3667	98.4292			
8	99.3969	99.3085	99.4059	99.3078			
9	99.2110	99.1204	99.1587	99.0774			
10	98.8394	98.5198	98.7985	98.7467			
11	98.9706	99.0593	99.0224	98.9975			
12	99.0425	99.0592	99.0944	98.9633			
13	99.1072	98.8357	99.0167	98.9584			
14	99.0121	98.9175	98.9514	98.8717			
15	99.0650		98.9610	98.9082	97.1087	98.6133	98.6654
16	99.0472		98.9007	98.8719	98.6259	98.5634	
17	99.1902		99.0789	99.0568	98.9996		
18	99.2656		99.3488	99.2322	99.0923	99.0771	
19	99.3073		99.2641	99.2157	98.8992	99.0655	
20	98.9758		98.9151	98.8217	98.8308	98.5748	98.6104
5°C							

Table 4a: SEC Percent Monomer at 5°C

-19-

Formulation No.	T = 0	2M	3M
1	99.0355	98.6402	98.8019
2	99.2563	99.1662	99.2864
3	99.3694	99.3403	99.3223
4	98.6003	98.2548	98.4045
5	99.1434	98.9114	99.1387
6	98.7584	98.5717	98.6349
7	98.6183	98.2416	98.2972
8	99.3969	99.2150	99.3074
9	99.2110	99.0286	99.1042
10	98.8394	98.7129	98.7604
11	98.9706	98.9305	98.9714
12	99.0425	98.9368	99.1233
13	99.1072	98.8489	98.9685
14	99.0121	98.8378	98.8908
15	99.0650		
16	99.0472		
17	99.1902		
18	99.2656		
19	99.3073		
20	98.9758		
15°C			

Table 4b: SEC Percent Monomer at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	99.0355	98.7580	98.5574	98.4367	98.0368
2	99.2563	99.1589	99.1105	99.0405	98.5627
3	99.3694	99.1199	99.2184	99.2363	98.5666
4	98.6003	98.2757	98.0982	97.9622	97.6140
5	99.1434	98.8306	98.8633	98.9352	98.6050
6	98.7584	98.5073	98.3420	98.2210	97.9763
7	98.6183	98.1165	97.7388	97.8497	97.4158
8	99.3969	99.2152	98.9631	99.0373	98.6140
9	99.2110	98.9730	98.5146	98.5381	97.9131
10	98.8394	98.3577	98.3127	98.2688	97.7979
11	98.9706	98.7703	98.4922	98.3596	97.7233
12	99.0425	98.9297	98.7366	98.9000	98.4723
13	99.1072	98.8193	98.5467	98.3160	97.6511
14	99.0121	98.8272	98.5284	98.5095	97.9758
15	99.0650	98.8577		98.5196	
16	99.0472	98.6574		98.4515	
17	99.1902	98.8746		98.7144	

-20-

Formulation No.	T = 0	1M	2M	3M	6M
18	99.2656	99.2270		99.1250	
19	99.3073	99.1136		99.0706	
20	98.9758	98.7749		98.5271	
25°C					

Table 4c: SEC Percent Monomer at 25°C

Formulation No.	T = 0	0.5M	1M	2M	3M
1	99.0355		98.4677	97.9971	97.7652
2	99.2563		99.0013	98.7378	98.6375
3	99.3694		99.1080	98.7451	98.3767
4	98.6003		97.8095	97.5004	97.0372
5	99.1434		98.8166	98.5338	98.5051
6	98.7584		98.3243	97.9466	97.8319
7	98.6183		97.8843	97.4690	97.1288
8	99.3969		98.9599	98.4933	98.0880
9	99.2110		98.5422	97.9500	97.4241
10	98.8394		98.3525	97.4123	97.1977
11	98.9706		98.3487	97.5550	97.0332
12	99.0425		98.8261	98.4669	98.5462
13	99.1072		98.3253	97.5610	96.9009
14	99.0121		98.4796	98.0903	97.4965
15	99.0650	98.6582	98.4581	97.9458	97.4352
16	99.0472	98.7509	98.4086	97.7286	97.5245
17	99.1902	98.9399	98.6580		98.0500
18	99.2656	99.1655	99.0648		98.7695
19	99.3073	99.0714	99.0123		98.5604
20	98.9758	98.8358	98.4525		97.3536
35°C					

Table 4d: SEC Percent Monomer at 35°C

5 Formulation Study A: Results - Charge Heterogeneity- iCIEF

a) Percent Main Peak

iCIEF percent main peak values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 5a-5d**. Initial values for main peak conditions were between 76.2 and 77.9% for all of the formulations. The rate main peak degradation correlates with increasing temperature. Degradation is minimal over 18 months at 5°C where the percent main peak remaining is above 75%.

-21-

An apparent E_a estimate of 21.5 kcal/mol was used for predictions. 24-month peak predictions at 5°C were made for percent change as a function of the five input variables (based on data up to three months). The effects of the five input variables are largest for pH though still below a < 2% difference. The only two input variables which exhibited a statistically significant effect were pH and NaCl concentrations. Increased NaCl concentration appears to result in increased main peak percent. Optimal stability for pH occurs between 5.5 and 6.0. Polysorbate 80, mirikizumab concentration and container closure display no clear effects across the region studied.

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	76.249	76.457	77.4974	77.0197			
2	76.771	76.0299	78.0262	77.194			
3	77.483	77.5245	77.247	76.7673			
4	76.814	76.6595	77.6503	76.8323			
5	76.932	78.1101	77.5302	78.0785			
6	76.979	76.4634	77.6098	77.9768			
7	77.885	77.0024	76.8658	77.2929			
8	77.347	77.8472	76.4671	76.9217			
9	77.319	75.8231	77.7577	76.7761			
10	77.65	77.0708	77.5101	76.3533			
11	77.464	76.7833	76.7427	76.7959			
12	77.491	77.6075	77.3274	76.9652			
13	77.188	76.9076	77.352	76.3947			
14	76.358	78.3481	78.3347	77.7161			
15	76.857		76.9503	76.6911	75.9130	75.1500	75.6132
16	77.479		77.7609	77.1041	76.3997	75.3519	
17	76.489		77.5801	77.4066	76.3635		
18	77.229		76.6101	76.7367	75.8246	75.9435	
19	77.164		77.0661	76.7541	77.0427	75.8500	
20	76.406		77.7999	76.865	76.4249	75.6967	75.7152
5°C							

Table 5a: iCIEF percent main peak values at 5°C

Formulation No.	T = 0	2M	3M
1	76.249	77.018	77.1088
2	76.771	76.7464	76.5012
3	77.483	77.2721	75.7589
4	76.814	76.8649	76.7558

-22-

Formulation No.	T = 0	2M	3M
5	76.932	76.3058	76.3988
6	76.979	76.9648	77.0176
7	77.885	76.2023	77.0162
8	77.347	76.8247	75.5478
9	77.319	75.8862	75.6762
10	77.65	76.1686	76.7645
11	77.464	76.156	76.8353
12	77.491	76.4543	77.2787
13	77.188	75.5027	75.9949
14	76.358	76.1096	76.2348
15	76.857		
16	77.479		
17	76.489		
18	77.229		
19	77.164		
20	76.406		
15°C			

Table 5b: iCIEF percent main peak values at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	76.2494	74.6671	72.7393	71.2816	64.7192
2	76.7706	75.4796	73.4600	71.2311	65.4286
3	77.4833	73.9273	73.1827	69.6172	61.7551
4	76.8135	74.9208	73.1140	71.2334	64.8606
5	76.9318	73.9897	74.2049	71.9191	65.7880
6	76.9791	75.0849	72.6246	71.9830	65.5446
7	77.8846	74.7839	73.5302	71.4002	65.4577
8	77.3469	73.2836	71.7735	69.9805	61.5478
9	77.3187	74.2636	70.7556	69.8180	61.0473
10	77.6495	74.5217	73.6534	71.5473	65.0711
11	77.4639	74.4789	71.2874	70.0361	62.8683
12	77.4914	74.1786	73.1139	70.9370	63.8732
13	77.1884	73.4831	72.3973	69.1369	61.6577
14	76.3577	74.8848	73.5164	71.2579	65.2474
15	76.8571	74.3107		71.6996	
16	77.4791	73.7653		72.2290	
17	76.4893	73.9362		71.5315	
18	77.2288	73.5806		71.2250	
19	77.1640	73.8950		70.9544	
20	76.4055	73.3600		71.4613	

-23-

Formulation No.	T = 0	1M	2M	3M	6M
25°C					

Table 5c: iCIEF percent main peak values at 25°C

-24-

Formulation No.	T = 0	0.5M	1M	2M	3M
1	76.2494		70.8149	64.7660	59.6243
2	76.7706		69.2740	63.5148	57.8644
3	77.4833		67.8585	62.9347	55.9226
4	76.8135		68.4201	63.6150	57.7644
5	76.9318		69.4003	64.9376	59.4563
6	76.9791		69.0681	63.5995	59.8020
7	77.8846		69.7444	63.9882	58.9208
8	77.3469		69.2564	62.0311	55.6978
9	77.3187		67.7674	59.5781	54.6138
10	77.6495		69.7079	63.3486	59.3782
11	77.4639		69.0436	60.9575	55.8693
12	77.4914		68.6143	61.6463	56.4150
13	77.1884		68.9236	60.1417	55.8102
14	76.3577		70.4030	62.8651	58.3541
15	76.8571	74.4201	69.6664	63.8884	58.5500
16	77.4791	74.1040	69.4573	63.5327	58.6029
17	76.4893	75.5326	69.0237		58.2574
18	77.2288	75.3470	69.7868		57.8872
19	77.1640	75.4974	68.5918		58.0911
20	76.4055	75.6802	69.2072		58.1669
35°C					

Table 5d: iCIEF percent main peak values at 35°C

b) Acidic and Basic Variants

Total acidic variants values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 6a-6d**. Total basic variants values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 6e-6h**.

Acidic variants increased over the course of the 18 months of data collected while only very small changes in basic variants over time were observed, except at 35°C. Acidic variants trends mirror main peak behaviour with increasing temperature causing increased acidic variant formation. Acidic variants likely arise primarily from deamidation.

Similar to the data for the main peak, the effects of all the input variables on 24-month change predictions for acidic variants and basic variants are < 1%. The largest effect is derived from pH but the trends are different between the two variant forms. Acidic variants appears more stable closer to pH 5.5 while percent basic variants is most

-25-

stable at pH 6.0. These two distinct trends combine to result in pH environments between pH 5.5 and 6.0 being the most chemically stable for the antibody.

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	20.4055	21.631	20.3655	20.3052			
2	20.1449	22.2292	19.7861	20.2322			
3	19.823	20.6944	20.7415	20.4157			
4	20.054	21.5949	20.4933	20.5673			
5	20.4103	20.2037	20.602	19.7644			
6	19.9079	21.8889	20.419	19.607			
7	19.794	21.0742	21.1869	20.0436			
8	19.974	20.3869	21.4964	20.4254			
9	19.8943	22.1758	20.2005	20.2884			
10	19.6687	21.0487	20.3686	20.27			
11	19.8394	21.2916	21.2626	20.5052			
12	19.7735	20.7711	20.5465	20.2354			
13	19.6189	21.0768	20.5447	20.6569			
14	20.198	19.9731	19.7427	19.7391			
15	19.9483		21.1069	20.6159	20.9791	21.7175	21.457
16	19.8828		20.1741	20.2382	20.6372	21.2031	
17	19.9751		20.428	19.9204	20.6318		
18	20.0091		21.4877	20.5752	21.2144	21.1288	
19	20.0874		21.0655	20.7643	20.1138	21.0979	
20	20.239		20.1953	20.3298	20.6988	21.2257	21.5033
5°C							

Table 6a: Total acidic variants at 5°C

5

Formulation No.	T = 0	2M	3M
1	20.4055	21.0943	20.7038
2	20.1449	21.4529	21.2562
3	19.823	20.8163	21.8499
4	20.054	21.3845	21.3757
5	20.4103	21.8369	21.6883
6	19.9079	21.2826	20.8413
7	19.794	21.6961	20.8314
8	19.974	21.3031	22.0992
9	19.8943	22.0056	21.8584
10	19.6687	21.8855	21.0284
11	19.8394	21.8157	20.7399
12	19.7735	21.7569	20.7732

-26-

Formulation No.	T = 0	2M	3M
13	19.6189	22.3371	21.732
14	20.198	21.9349	21.6673
15	19.9483		
16	19.8828		
17	19.9751		
18	20.0091		
19	20.0874		
20	20.239		
15°C			

Table 6b: Total acidic variants at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	20.4055	23.1548	25.0098	25.8025	31.2538
2	20.1449	22.4288	24.2000	25.9315	31.2603
3	19.8230	23.4027	24.2329	26.8533	33.5964
4	20.0540	22.8982	24.7868	26.4475	32.8154
5	20.4103	23.7062	23.7564	25.6761	31.6880
6	19.9079	22.8971	25.2966	25.6665	31.9319
7	19.7940	23.1534	24.2692	26.2355	32.0976
8	19.9740	23.9852	25.5711	26.6401	33.8217
9	19.8943	23.2700	26.5403	26.8297	34.1044
10	19.6687	23.1443	23.9993	25.5189	30.9147
11	19.8394	23.0846	25.8232	26.5416	32.4278
12	19.7735	23.8236	24.9009	26.5619	33.6655
13	19.6189	24.2774	25.0257	26.8501	34.0237
14	20.1980	22.9632	24.1213	25.4142	31.3472
15	19.9483	23.5511		25.0755	
16	19.8828	24.0707		24.6124	
17	19.9751	23.8232		25.2383	
18	20.0091	23.9931		25.5718	
19	20.0874	23.7843		25.9072	
20	20.2390	24.6158		25.4013	
25°C					

Table 6c: Total acidic variants at 25°C

-27-

Formulation No.	T = 0	0.5M	1M	2M	3M
1	20.4055		26.3088	32.2593	36.5812
2	20.1449		27.7793	33.5659	38.2329
3	19.8230		28.5428	33.1278	37.3047
4	20.0540		29.1631	34.1725	40.0308
5	20.4103		28.1070	32.8886	38.1781
6	19.9079		28.6558	34.1987	37.7237
7	19.7940		27.9910	33.7899	38.5636
8	19.9740		27.5633	34.0322	37.7201
9	19.8943		28.9933	36.6182	39.2168
10	19.6687		27.6328	33.5580	36.9741
11	19.8394		27.7042	35.2747	37.7605
12	19.7735		29.1395	36.2954	41.2850
13	19.6189		28.0042	36.2388	38.3822
14	20.1980		26.7329	34.3455	37.3287
15	19.9483	22.8539	27.5238	33.1436	37.1002
16	19.8828	23.1756	27.8511	33.4211	37.0848
17	19.9751	21.6397	28.1958		38.2614
18	20.0091	21.9780	27.3211		38.5680
19	20.0874	21.8929	28.3091		38.5784
20	20.2390	21.5311	28.0253		38.2532
35°C					

Table 6d: Total acidic variants at 35°C

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	3.3451	1.9119	2.1371	2.6751			
2	3.0845	1.7409	2.1877	2.5738			
3	2.6937	1.7811	2.0115	2.817			
4	3.1325	1.7456	1.8564	2.6004			
5	2.6578	1.6862	1.8678	2.1571			
6	3.1131	1.6476	1.9712	2.4162			
7	2.3214	1.9234	1.9473	2.6635			
8	2.6791	1.7659	2.0365	2.6529			
9	2.787	2.0011	2.0418	2.9355			
10	2.6818	1.8806	2.1212	3.3767			
11	2.6967	1.9252	1.9948	2.6989			
12	2.7351	1.6214	2.1261	2.7994			
13	3.1926	2.0156	2.1033	2.9484			
14	3.4443	1.6788	1.9227	2.5448			
15	3.1947		1.9428	2.6929	3.1079	3.1325	2.9299
16	2.6381		2.065	2.6577	2.9631	3.445	

-28-

17	3.5356		1.9919	2.673	3.0047		
18	2.7621		1.9022	2.6881	2.9610	2.9277	
19	2.7485		1.8684	2.4816	2.8435	3.0521	
20	3.3555		2.0048	2.8053	2.8764	3.0776	2.7815
5°C							

Table 6e: Total basic variants at 5°C

Formulation No.	T = 0	2M	3M
1	3.3451	1.8877	2.1874
2	3.0845	1.8007	2.2426
3	2.6937	1.9116	2.3912
4	3.1325	1.7506	1.8685
5	2.6578	1.8572	1.9129
6	3.1131	1.7525	2.141
7	2.3214	2.1016	2.1524
8	2.6791	1.8722	2.3529
9	2.787	2.1082	2.4655
10	2.6818	1.9459	2.2071
11	2.6967	2.0282	2.4248
12	2.7351	1.7888	1.9481
13	3.1926	2.1603	2.2731
14	3.4443	1.9555	2.0979
15	3.1947		
16	2.6381		
17	3.5356		
18	2.7621		
19	2.7485		
20	3.3555		
15°C			

Table 6f: Total basic variants at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	3.3451	2.1780	2.2509	2.9159	4.0270
2	3.0845	2.0917	2.3400	2.8374	3.3111
3	2.6937	2.6700	2.5844	3.5295	4.6485
4	3.1325	2.1810	2.0992	2.3191	2.3240
5	2.6578	2.3041	2.0387	2.4048	2.5240
6	3.1131	2.0179	2.0788	2.3506	2.5235
7	2.3214	2.0627	2.2006	2.3642	2.4447
8	2.6791	2.7312	2.6554	3.3794	4.6305

-29-

Formulation No.	T = 0	1M	2M	3M	6M
9	2.7870	2.4663	2.7042	3.3523	4.8483
10	2.6818	2.3341	2.3473	2.9338	4.0142
11	2.6967	2.4365	2.8894	3.4223	4.7039
12	2.7351	1.9978	1.9852	2.5012	2.4613
13	3.1926	2.2395	2.5771	4.0130	4.3186
14	3.4443	2.1520	2.3623	3.3279	3.4054
15	3.1947	2.1382		3.2249	
16	2.6381	2.1640		3.1587	
17	3.5356	2.2406		3.2302	
18	2.7621	2.4264		3.2031	
19	2.7485	2.3206		3.1384	
20	3.3555	2.0242		3.1374	
25°C					

Table 6g: Total basic variants at 25°C

Formulation No.	T = 0	0.5M	1M	2M	3M
1	3.3451		2.8763	2.9747	3.7945
2	3.0845		2.9467	2.9194	3.9027
3	2.6937		3.5987	3.9375	6.7727
4	3.1325		2.4168	2.2125	2.2048
5	2.6578		2.4927	2.1738	2.3656
6	3.1131		2.2760	2.2018	2.4743
7	2.3214		2.2646	2.2218	2.5156
8	2.6791		3.1804	3.9368	6.5822
9	2.7870		3.2393	3.8037	6.1695
10	2.6818		2.6593	3.0934	3.6478
11	2.6967		3.2522	3.7677	6.3701
12	2.7351		2.2461	2.0583	2.3000
13	3.1926		3.0722	3.6195	5.8076
14	3.4443		2.8641	2.7894	4.3173
15	3.1947	2.7260	2.8098	2.9680	4.3499
16	2.6381	2.7204	2.6916	3.0461	4.3123
17	3.5356	2.8277	2.7805		3.4812
18	2.7621	2.6751	2.8921		3.5449
19	2.7485	2.6097	3.0991		3.3305
20	3.3555	2.7887	2.7675		3.5798
35°C					

Table 6g: Total basic variants at 35°C

Formulation Study A: Results - CE-SDS

The CE-SDS reduced percent purity values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 7a-7d**.

An apparent increase in purity is observed for Formulations 15, 16, 19 and 20 from initial to three months at 5°C, which may be attributable to formulation to formulation variability. Those increases suggest that changes at 35°C may be somewhat masked by the same systematic variability. Nonetheless, significant changes were not observed at 5°C through 18 months and the overall changes after 3 months at 35°C were < 3%. With the high purity levels, both fragments and aggregates were low over the course of the study.

Projections of change in percent purity by reduced CE-SDS at 24-months with 5°C storage have large uncertainty compared to the input variable trends. Protein concentration was the only statistically significant effect. All projections of purity across the study range at 24-months at 5°C were < 1% different from the initial value.

The CE-SDS non-reduced percent purity values at 5°C, 15°C, 25°C and 35°C are shown in **Tables 7e-7h**.

Similar to reduced CE-SDS, systematic variation appears to play a role in the results with apparent increases at 5°C and 25°C. The increases suggest that changes at 35°C may be somewhat masked by the same systematic variability. Nonetheless, significant changes were not observed at 5°C through 18 months and the overall change after 3 months at 35°C was < 2%, similar to the reduced CE-SDS results. Aggregates did not show any trend over the course of the study; however, fragments increased at 35°C commensurate with decreasing purity. Among the input variables affecting percent purity by non-reduced CE-SDS, only antibody concentration and container closure were significant. The highest predicted purity is at pH 5.5. In all cases the effects of the input variables was < 1.2% differences for the 24-month predictions.

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	97.5507	98.3801	98.2813	97.8105			
2	97.0649	97.9730	98.1546	97.3604			
3	97.4520	97.3232	98.4907	98.1145			
4	97.8276	97.7769	97.6886	97.8431			
5	97.3942	98.1589	98.1053	98.2212			

-31-

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
6	97.6574	97.9765	98.2326	97.8587			
7	97.7581	97.1208	98.0067	97.8804			
8	97.4817	98.0293	98.1535	98.1867			
9	97.5403	98.0302	98.3630	98.1409			
10	97.1064	97.4358	97.0964	97.3349			
11	97.6548	97.3224	97.6726	97.7144			
12	97.1614	97.9483	97.8011	98.2771			
13	96.8327	97.5945	97.5611	98.0268			
14	97.1090	98.0629	98.2487	97.7208			
15	96.5847		98.3037	97.9695	97.8395	98.4964	98.4781
16	96.6236		98.2054	98.3130	97.8339	98.4941	
17	96.7342		98.0134	97.8475	97.8335		
18	97.2292		97.9314	98.2601	97.8416	98.7277	
19	97.4575		97.5617	98.1721	98.3135	98.6121	
20	96.8655		98.2118	98.3956	98.2908	98.3615	98.3379
5°C							

Table 7a: CE-SDS Reduced Percent Purity at 5°C

Formulation No.	T = 0	2M	3M
1	97.5507	98.3820	98.1285
2	97.0649	98.1436	97.9645
3	97.4520	97.4879	97.4027
4	97.8276	96.9612	97.2842
5	97.3942	97.5050	97.5497
6	97.6574	98.1696	97.2563
7	97.7581	97.2690	97.3688
8	97.4817	97.3503	97.3382
9	97.5403	98.1889	97.7139
10	97.1064	97.3433	97.4570
11	97.6548	97.3961	97.3463
12	97.1614	97.8991	96.8943
13	96.8327	97.1631	97.9515
14	97.1090	97.9360	97.9554
15	96.5847		
16	96.6236		
17	96.7342		
18	97.2292		
19	97.4575		
20	96.8655		

Table 7b: CE-SDS Reduced Percent Purity at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	97.5507	97.7180	97.8983	97.3789	97.0024
2	97.0649	97.5295	97.7062	97.3984	96.7571
3	97.4520	97.0034	97.2020	97.6527	96.0575
4	97.8276	97.3606	96.0053	97.2650	96.6949
5	97.3942	96.5218	97.3548	97.1520	96.3050
6	97.6574	97.2236	97.3712	96.6710	97.1334
7	97.7581	97.4982	96.8666	96.9829	96.8200
8	97.4817	96.9037	97.0056	97.0508	96.4313
9	97.5403	97.5925	97.9648	97.2853	97.0312
10	97.1064	97.1357	97.4201	97.2028	97.0236
11	97.6548	97.4292	96.9086	97.6319	96.6932
12	97.1614	97.1620	97.7703	97.1905	96.7637
13	96.8327	97.2394	96.9971	97.0322	96.0957
14	97.1090	97.3834	97.8225	97.4674	97.0869
15	96.5847	97.3145		97.6546	
16	96.6236	97.1901		97.6555	
17	96.7342	97.5599		96.9369	
18	97.2292	97.1179		96.4945	
19	97.4575	97.0371		96.1859	
20	96.8655	96.9908		97.5514	
25°C					

Table 7c: CE-SDS Reduced Percent Purity at 25°C

Formulation No.	T = 0	0.5M	1M	2M	3M
1	97.5507	97.5507	96.9313	97.2870	96.1532
2	97.0649		97.4753	97.1694	96.0687
3	97.4520		97.2477	96.7304	94.4314
4	97.8276		96.7039	95.6662	95.9299
5	97.3942		96.9681	96.9821	95.0054
6	97.6574		97.1291	97.1258	96.1740
7	97.7581		96.9738	95.7715	95.6826
8	97.4817		96.5674	96.3917	95.4628
9	97.5403		96.7375	96.9175	95.4513
10	97.1064		96.7377	95.9065	95.6888
11	97.6548		96.8034	95.6240	94.9063
12	97.1614		96.8655	96.7924	95.9932
13	96.8327		95.9288	95.5828	95.0787
14	97.1090		96.8665	97.0749	96.0751
15	96.5847	97.7067	97.4548	96.9007	95.9292

-33-

Formulation No.	T = 0	0.5M	1M	2M	3M
16	96.6236	97.4524	97.6586	96.2392	96.0330
17	96.7342	97.5060	97.3783		95.6949
18	97.2292	97.1765	96.8734		95.8199
19	97.4575	97.0326	96.5486		96.1470
20	96.8655	97.6592	96.3710		95.6133
35°C					

Table 7d: CE-SDS Reduced Percent Purity at 35°C

Formulation No.	T = 0	2M	3M	6M	9M	12M	18M
1	96.9039	96.8445	98.3621	98.2040			
2	97.2975	97.4588	98.5629	98.3824			
3	97.3447	96.9632	98.4322	98.2835			
4	96.5918	96.6834	98.0780	98.0484			
5	97.0705	97.0721	98.4007	98.4233			
6	96.6047	96.7245	98.1683	98.0190			
7	96.9997	96.5277	97.4261	97.6353			
8	97.3593	97.1098	98.3761	98.2971			
9	97.0338	96.9290	98.2217	98.2390			
10	96.9411	96.8050	98.0318	97.8740			
11	97.4093	97.0486	97.8660	98.0523			
12	97.0490	96.9274	98.2431	98.1285			
13	96.9942	96.6767	98.1622	98.0213			
14	97.3837	97.1616	98.1614	98.1674			
15	96.7366		98.2045	98.0093	97.9696	98.3218	98.2038
16	96.7732		97.9185	98.0947	97.7699	98.1218	
17	96.9295		98.0719	98.2230	97.9286		
18	96.4994		98.2993	98.2364	98.0584	98.1484	
19	96.6090		98.4547	98.2275	98.0079	98.1526	
20	96.7352		97.8862	97.7883	97.6347	98.3966	97.6906
5°C							

Table 7e: CE-SDS Non-Reduced Percent Purity at 5°C

Formulation No.	T = 0	2M	3M
1	96.9039	96.9712	97.9656
2	97.2975	96.9043	98.2914
3	97.3447	96.9133	98.1891
4	96.5918	96.6237	97.6884
5	97.0705	96.6024	98.4309
6	96.6047	96.4388	98.1833

-34-

Formulation No.	T = 0	2M	3M
7	96.9997	96.3301	97.9220
8	97.3593	97.2064	98.4813
9	97.0338	96.9656	98.0428
10	96.9411	96.9155	98.1686
11	97.4093	97.0499	97.8849
12	97.0490	96.8346	98.5873
13	96.9942	96.8063	98.2052
14	97.3837	97.1529	98.3782
15	96.7366		
16	96.7732		
17	96.9295		
18	96.4994		
19	96.6090		
20	96.7352		

Table 7f: CE-SDS Non-Reduced Percent Purity at 15°C

Formulation No.	T = 0	1M	2M	3M	6M
1	96.9039	96.2471	96.4737	97.5694	95.5840
2	97.2975	96.4607	96.8826	97.8304	96.2792
3	97.3447	96.1175	96.8708	97.7204	96.0670
4	96.5918	95.3576	96.7694	97.3853	96.0533
5	97.0705	96.2991	96.4733	97.4408	96.4844
6	96.6047	95.7491	96.4820	97.2507	96.1573
7	96.9997	95.7407	95.9558	97.1083	95.5777
8	97.3593	96.3300	95.0148	97.4844	95.8544
9	97.0338	96.0932	96.3993	97.3921	95.5305
10	96.9411	95.7323	96.1893	97.2104	95.7931
11	97.4093	95.6305	95.6457	96.9553	95.0774
12	97.0490	96.2159	95.9127	97.5745	96.3215
13	96.9942	95.5777	95.9239	97.0908	95.2201
14	97.3837	95.7672	95.9141	97.6085	95.8315
15	96.7366	95.7577		97.3223	
16	96.7732	95.4891		97.2359	
17	96.9295	95.7314		97.5411	
18	96.4994	96.0733		97.7533	
19	96.6090	96.0170		97.7403	
20	96.7352	95.9756		97.6437	
25°C					

Table 7g: CE-SDS Non-Reduced Percent Purity at 25°C

-35-

Formulation No.	T = 0	0.5M	1M	2M	3M
1	96.9039		95.4541	95.7214	95.9955
2	97.2975		96.6302	96.4868	96.4840
3	97.3447		96.1415	94.0588	95.1660
4	96.5918		95.5678	95.2637	95.7324
5	97.0705		95.8169	95.1633	95.8433
6	96.6047		95.7668	95.5797	95.9383
7	96.9997		95.3829	94.9754	95.0895
8	97.3593		96.0538	94.6394	95.0156
9	97.0338		95.9438	94.9243	94.7194
10	96.9411		96.0586	95.0894	95.5331
11	97.4093		95.8688	94.8264	94.1685
12	97.0490		95.9639	95.9096	96.3749
13	96.9942		95.6145	94.8611	94.9630
14	97.3837		95.6307	95.4842	96.0973
15	96.7366	96.7627	95.9200	95.0685	95.8148
16	96.7732	96.5548	95.6335	94.9967	95.6304
17	96.9295	96.6883	95.5187		95.5805
18	96.4994	95.0636	95.7580		95.8685
19	96.6090	95.8628	95.6329		95.6578
20	96.7352	96.6232	95.7850		95.2232
35°C					

Table 7h: CE-SDS Non-Reduced Percent Purity at 35°C

Formulation Study A: Results - Subvisible Particles**a) HIAC**

5 The data from HIAC subvisible particle testing at 5°C, 15°C, 25°C and 35°C is shown in **Tables 8a-8d**.

Most formulations at 25°C through 3 months have counts below 5000, which is within the acceptable range for subvisible counts in a prefilled syringe. Formulation Nos. 4, 7, 10, 11 and 13 have values that are well in excess of this count. These formulations are the five formulations that have an antibody target concentration of 150 mg/mL. The next closest formulation in terms of less than 2µm/mL counts is Formulation No. 16, which has an antibody concentration of 125 mg/mL. Formulation No. 4 has the greatest number of particles and the highest values are not fully reliable as they exceed the qualified range of the instrument. Subvisible counts at an antibody concentration of 150 mg/mL are also higher than other runs at 5°C but the trend is more pronounced at

-36-

25°C. Notably, Formulation Nos. 4, 7, 10, 11 and 13 still conform to USP <788> count/container requirements throughout the study apart from the 3-month 35°C time point.

Formulation No.	T = 0	3M	12M	18M
1	2066	1628		
2	1237	3309		
3	1289	2033		
4	15438	15563		
5	1285	2089		
6	1124	2898		
7	10346	15101		
8	2958	1631		
9	1655	959		
10	7644	7461		
11	8549	11140		
12	1903	2568		
13	9961	4161		
14	2402	1469		
15	1470	1096	1890	4269
16	3394	1815	951	
17	199	284		
18	182	826	3002	
19	215	683		
20	3545	3056	2779	8107
5°C				

5

Table 8a: HIAC less than or equal to 2µm counts/mL at 5°C

Formulation No.	T = 0	3M
1	2066	984
2	1237	2362
3	1289	1358
4	1543	20270
5	1285	1388
6	1124	5494
7	1034	8260
8	2958	2078
9	1655	1053
10	7644	11392
11	8549	7273
12	1903	2259

-37-

Formulation No.	T = 0	3M
13	9961	9403
14	2402	1522
15	1470	
16	3394	
17	199	
18	182	
19	215	
20	3545	
5°C		

Table 8b: HIAC less than or equal to 2µm counts/mL at 15°C

Formulation No.	T = 0	1M	3M
1	2066	1448	1294
2	1237	3486	1708
3	1289	1834	1896
4	1543	32874	39721
5	1285	1856	1547
6	1124	4729	2015
7	1034	12181	7313
8	2958	1784	3614
9	1655	1371	3001
10	7644	6200	3307
11	8549	4977	11507
12	1903	5037	3280
13	9961	5323	16237
14	2402	2750	2461
15	1470	2919	1422
16	3394	3363	5602
17	199	332	403
18	182	335	227
19	215	490	1256
20	3545	3105	3743
25°C			

Table 8c: HIAC less than or equal to 2 µm counts/mL at 25°C

-38-

Formulation No.	T = 0	1M	3M
1	2066	1157	2880
2	1237	1317	2582
3	1289	2258	4423
4	1543	23054	43613
5	1285	2070	1992
6	1124	2604	4533
7	1034	8965	18476
8	2958	2911	8252
9	1655	1980	5162
10	7644	20558	34576
11	8549	9866	29565
12	1903	3500	3693
13	9961	20738	28594
14	2402	5691	1949
15	1470	2889	3740
16	3394	2492	4543
17	199	507	1581
18	182	514	1153
19	215	685	2205
20	3545	4855	8602
35°C			

Table 8d: HIAC less than or equal to 2µm counts/mL at 25°C

b) MFI

The data from MFI subvisible particle testing at 5°C, 15°C, 25°C and 35°C is shown in **Tables 8e-8g**.

Similar trends were observed with MFI results as compared to HIAC results. At 25°C, the highest counts across all of the formulations correspond to those with an antibody concentration of 150 mg/mL. Unlike HIAC results, Formulation No. 16 counts were comparable to those of lower antibody concentration formulations. Formulation No. 4 again showed the highest counts (nearly an order of magnitude higher than other formulations).

-39-

Formulation No.	T = 0	3M	6M	18M
1	1316	4437		
2	5718	31942	9000	
3	8812	6348	11010	
4	151896	159322		
5	6748	4689	3116	
6	7006	16263		
7	80650	48541		
8	17001	5683	2526	
9	933	2386		
10	24888	26509		
11	29499	40247		
12	27221	11188		
13	38049	8242		
14	5480	2218		
15	1038	2035		64155
16	3158			
17	9250	1332		
18	5417	5500		
19	2737	2584		
20	1796	5164		3940
5°C				

Table 8e: MFI less than or equal to 2µm counts/mL at 5°C

Formulation No.	T = 0	3M	6M
1	1316	2028	8496
2	5718	4630	11086
3	8812	12999	9110
4	151896	454681	805017
5	6748	9283	32884
6	7006	11535	10671
7	80650	30786	73491
8	17001	11595	17139
9	933	7622	9875
10	24888	8900	23889
11	29499	23468	
12	27221	16450	20885
13	38049	72204	41426
14	5480	4936	13277
15	1038	4995	
16	3158	5791	
17	9250	3649	
18	5417	4114	

-40-

19	2737	2866	
20	1796		
25°C			

Table 8f: MFI less than or equal to 2µm counts/mL at 25°C

Formulation No.	T = 0	3M
1	1316	14816
2	5718	15479
3	8812	
4	151896	447247
5	6748	5677
6	7006	68495
7	80650	116643
8	17001	26143
9	933	19053
10	24888	371523
11	29499	98003
12	27221	12521
13	38049	119192
14	5480	5572
15	1038	12973
16	3158	12246
17	9250	
18	5417	
19	2737	
20	1796	
35°C		

Table 8g: MFI less than or equal to 2µm counts/mL at 35°C

5 Formulation Study A: Conclusions

The purpose of Formulation Study A was to identify a formulation composition suitable for administration to human patients and to monitor the robustness of the formulation by systematically optimizing the critical formulation parameters with respect to stability properties. In this study, physical and chemical stability were evaluated as functions of mirikizumab concentration, pH, NaCl and polysorbate 80. Several formulations appear to be robust from a chemical and physical stability standpoint over the entire region studied with all 24-month at 5°C change projections < 5%. Optimal stability by SEC is closer to pH 5.0 (though the entire pH range had changes < 2% after 24-months at 5°C). iCIEF results indicated that optimal stability was between pH 5.5 and

-41-

pH 6.0. Other methods did not show clear trends for pH. Accounting for these projections, pH 5.5 is deemed to be the optimal pH since it balances the observations from both relevant assays. Increasing protein concentration did result in lower SEC percent monomer and lower non-reduced CE-SDS purity but the differences between 20
5 and 150 mg/mL were < 1%. No significant trends were observed in relation to changes in NaCl or polysorbate 80 concentrations. There were also no significant effects observed between container closure types in this study. Subvisible particle counts were higher in the formulations targeting 150 mg/mL of mirikizumab. Additional studies are being undertaken to better understand the causes of this observation. Based on results described
10 here, the preferred formulation is 10 mM citrate buffer, 150 mM NaCl, 0.03% w/v polysorbate 80 (0.05% w/v in vials for IV administration) at pH 5.5. For intravenous administration from vials, the preferred concentration of polysorbate 80 is 0.05% w/v.

Example 3: Formulation Study B

15 Purpose

It has been hypothesized that the presence of sodium chloride and/or citrate may increase the likelihood of injection site discomfort. The purpose of Formulation Study B is to identify an alternative formulation of mirikizumab that has a high probability of providing a well-tolerated injection experience. In addition to improving perceived
20 injection pain, other objectives of the study include: meeting standard bioequivalence criteria compared to the preferred formulation identified in Formulation Study A and maintaining and/or minimally perturbing the stability, manufacturability, and deliverability afforded by the preferred formulation.

25 Formulation Study B: Study design and preparation of anti-IL-23p19 antibody pharmaceutical formulations

Part I of the study comprised the design and assessment of a number of formulations as shown in **Table 9a**.

Formulation No.	Antibody (mg/mL)	Buffer	Excipients	Surfactant	pH ¹
1	125	10 mM citrate	150 mM NaCl	0.03% w/v PS80	5.5
21	125	5 mM citrate	5% w/v mannitol	0.03% w/v PS80	5.5
22	125	5 mM histidine	5% w/v mannitol	0.03% w/v PS80	5.6
23	125	5 mM histidine	5% w/v mannitol	0.03% w/v PS80	5.9
24	125	5 mM histidine	5% w/v mannitol	0.03% w/v PS80	6.2
25	125	10 mM histidine	37.5 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	5.5
26	125	10 mM histidine	75 mM NaCl 3.3% w/v mannitol	0.03% w/v PS80	5.5
27	125	5 mM histidine	9% w/v sucrose	0.03% w/v PS80	5.6
28	125	5 mM histidine	9% w/v trehalose	0.03% w/v PS80	5.6
29	125	self-buffered	5% w/v mannitol	0.03% w/v PS80	5.4

¹ Average of measured values across all stability conditions

Table 9a: Formulations assessed in Part A of Formulation Study B

With the exception of Formulation 1 (which is the preferred formulation from Formulation Study A), samples were prepared by buffer exchange of drug substance lot EL01685-056-F-Fill (C1 demo #2) into the matrices (without polysorbate 80) listed in **Table 9**. The buffer exchanged samples were concentrated and/or diluted with buffer to 125 mg/mL of mirikizumab, and spiked with polysorbate 80 (PS80) to a final concentration of 0.03% w/v. The formulations were then sterile filtered, filled into a 2.25

mL syringe, and the appropriate plunger inserted. The final drug product samples were stored and pulled from chambers as indicated in **Table 9b**.

Temperature (°C)	Time (weeks)					
	0	2	4	8	13	26
5	X		X		X	X
25			X	X	X	
40		X	X	X		

Table 9b: Part A Time Point and Temperature Conditions

- 5 The results from the assessment of the formulations shown in **Table 9a** led to design and assessment of further formulations as shown in **Table 10a** (Part II of the study).

Formulation No.	Antibody (mg/mL)	Buffer	Excipients	Surfactant	pH ¹
1	125	10 mM citrate	150 mM NaCl	0.03% w/v PS80	5.5
30	125	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	5.9
31	125	self-buffered	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	5.3
32	125	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	5.2
33	125	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	6.3
34	125	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	5.6
35	125	self-buffered	150 mM NaCl	0.03% w/v PS80	5.5
36	125	self-buffered	25 mM NaCl 4.1% w/v mannitol	0.03% w/v PS80	6.0

¹ Average of measured values across all stability conditions

Table 10a: Formulations assessed in Part B of Formulation Study B

With the exception of Formulation 1 (which is the preferred formulation from Formulation Study A), samples were prepared by buffer exchange (first against 0.3 M NaCl) of drug substance lot EL01685-056-F-Fill (C1 demo #2) against 0.3 M NaCl and then buffer exchanged further into the matrices (without polysorbate 80) listed in **Table 10a**. This two-step dialysis approach was used to limit the amount of residual citrate in the final drug product samples. The buffer exchanged samples were concentrated and/or diluted with buffer to 125 mg/mL of mirikizumab, and spiked with a PS80 to a final concentration of 0.03% w/v. The formulations were then sterile filtered, filled into a 2.25 mL syringe, and the appropriate plunger inserted. The final drug product samples were stored and pulled from chambers as indicated in **Table 10b**.

Temperature (°C)	Time (weeks)					
	0	2	4 ¹	8	13	26
5 ³	X			X	X	X
25			X	X	X ²	
35		X	X	X		

¹ Formulation 34 was submitted at week 5.

² Formulation 35 and Formulation 36 were submitted at week 14.

³ Formulation 35 and Formulation 36 were submitted only at weeks 0 and 4 (the 4 week data will not be presented for these formulations).

Table 10b: Part B Time Point and Temperature Conditions

The results from the assessment of the formulations shown in **Table 9a** and **Table 10a** led to design and assessment of further formulations as shown in **Table 11a** (Part III of the study).

-45-

Formulation No.	Antibody (mg/mL)	Buffer	Excipients	Surfactant	pH ¹	Drug Substance Lot
1	125	10 mM citrate	150 mM NaCl	0.03% w/v PS80	5.5	EL01685-056-F-Fill
37	125	self-buffered	75 mM NaCl, 2.5% w/v mannitol	0.03% w/v PS80	5.5	EL19481-008-F-Fill
38	125	self-buffered	75 mM NaCl, 2.5% w/v mannitol	0.03% w/v PS80	5.4	EL01685-056-F-Fill
39	125	5 mM histidine	30 mM NaCl, 3.9% w/v mannitol	0.03% w/v PS80	5.3	EL19481-007-F-Fill
40	125	5 mM histidine	50 mM NaCl, 3.3% w/v mannitol	0.03% w/v PS80	5.4	EL19481-007-F-Fill

1 Average of measured values across all stability conditions

Table 11a: Formulations assessed in Part C of Formulation Study B

5 With the exception of Formulation 1 (which is the preferred formulation from Formulation Study A), samples were prepared by buffer exchange or dilution of drug substance into the matrices (without polysorbate 80) listed in **Table 11a**. Formulation 38 was first dialyzed against 0.3 M NaCl. The samples were concentrated and/or diluted with buffer to 125 mg/mL of mirikizumab, and spiked with a PS80 to a final concentration of 0.03% w/v. The formulations were then sterile filtered, filled into the 2.25 mL syringe, and the appropriate plunger inserted. The final drug product samples were stored and pulled from chambers as indicated in **Table 11b**.

10

-46-

Temperature (°C)	Time (weeks)					
	0	2	4	8	12	26
5	X		X		X	X
25			X	X	X	
35		X ¹	X	X		

¹ Formulation 39 was not submitted at week 2.

Table 11b: Part C Time Point and Temperature Conditions

Formulation Study B: Part I Results - Purity

- 5 Both SEC and both CE-SDS methods showed a time- and temperature-dependent decrease in mirikizumab purity. All test formulations performed comparably to or better than the Formulation 1. The non-histidine containing matrices (Formulations 1, 21 and 29) displayed the largest decreases in purity over the course of the stability study. The SEC monomer purity degradation rates at 25°C and 40°C are shown in **Table 12**. The
- 10 non-histidine containing matrices (Formulations 1, 21 and 29) displayed the fastest degradation rates at the 25°C and 40°C conditions. Formulations 23 and 24 did not maintain solubility under refrigerated conditions.

-47-

Formulation No.	Buffer	Excipients	pH	Degradation Rate, 40°C (%/week)	R squared, 40°C	Degradation Rate, 25°C (%/week)	R squared, 25°C
1	10 mM citrate	150 mM NaCl	5.5	-0.3157	0.9980	-0.0370	0.9754
21	5 mM citrate	5% w/v mannitol	5.5	-0.2774	0.9952	-0.0286	0.9671
22	5 mM histidine	5% w/v mannitol	5.6	-0.2005	0.9980	-0.0219	0.9478
23	5 mM histidine	5% w/v mannitol	5.9	-0.1887	0.9991	-0.0261	0.9212
24	5 mM histidine	5% w/v mannitol	6.2	-0.1911	0.9993	-0.0275	0.8678
25	10 mM histidine	37.5 mM NaCl 4.1% w/v mannitol	5.5	-0.2299	0.9969	-0.0185	0.9527
26	10 mM histidine	75 mM NaCl 3.3% w/v mannitol	5.5	-0.2517	0.9900	-0.0231	0.9933
27	5 mM histidine	9% w/v sucrose	5.6	-0.2160	0.9933	-0.0197	0.8909
28	5 mM histidine	9% w/v trehalose	5.6	-0.2124	0.9977	-0.0201	0.9550
29	self-buffered	5% w/v mannitol	5.4	-0.3056	0.9934	-0.0390	0.9120

Table 12: SEC Monomer Purity Degradation Rates at Elevated Temperature

(The data was fit to a simple linear regression to determine a degradation rate)

Formulation Study B: Part I Results - Aggregates

5 SEC data showed a time- and temperature-dependent increase in mirikizumab aggregates. All formulations performed comparably to or better than Formulation 1. The non-histidine containing matrices (Formulations 1, 21, and 29) displayed the largest increases in aggregate over the course of the stability study. The SEC aggregates

-48-

formation rates at 25°C and 40°C are shown in **Table 13**. The non-histidine containing matrices (Formulations 1, 21, and 29) displayed the fastest degradation rates at the 25°C and 40°C conditions.

Formulation No.	Buffer	Excipients	pH	Formation Rate, 40°C (%/week)	R squared, 40°C	Formation Rate, 25°C (%/week)	R squared, 25°C
1	10 mM citrate	150 mM NaCl	5.5	0.2464	0.9864	0.0322	0.9901
21	5 mM citrate	5% w/v mannitol	5.5	0.2249	0.9936	0.0255	0.9980
22	5 mM histidine	5% w/v mannitol	5.6	0.1654	0.9907	0.0191	0.9673
23	5 mM histidine	5% w/v mannitol	5.9	0.1609	0.9968	0.0232	0.9631
24	5 mM histidine	5% w/v mannitol	6.2	0.1683	0.9991	0.0238	0.9178
25	10 mM histidine	37.5 mM NaCl 4.1% w/v mannitol	5.5	0.1756	0.9812	0.0153	0.9388
26	10 mM histidine	75 mM NaCl 3.3% w/v mannitol	5.5	0.1899	0.9825	0.0188	0.9559
27	5 mM histidine	9% w/v sucrose	5.6	0.1776	0.9824	0.0164	0.9791
28	5 mM histidine	9% w/v trehalose	5.6	0.1726	0.9900	0.0163	0.9966
29	self-buffered	5% w/v mannitol	5.4	0.2628	0.9972	0.0351	0.9531

Table 13: SEC Aggregates Formation Rates at Elevated Temperature

Formulation Study B: Part I Results – Fragments

The CE-SDS reduced fragments values are shown in **Table 14a** and the CE-SDS reduced fragments values are shown in **Table 14b**. Both CE-SDS methods showed a time- and temperature-dependent increase in mirikizumab fragments. All formulations performed comparably to or better than Formulation 1.

Formulation No.	Temp	5°C			25°C			40°C		
	T = 0	4w	13w	26w	4w	8w	13w	2w	4w	8w
1	0.31	0.33	0.26	0.50	0.42	0.46	0.89	1.52	2.39	4.10
21	0.37	0.25	0.33	0.44	0.39	0.53	0.88	1.28	2.22	3.89
22	0.25	0.24	0.25	0.32	0.65	0.43	0.88	1.12	2.07	3.50
23	0.31	0.21	0.32	0.43	0.65	0.68	0.88	1.12	1.78	3.35
24	0.34	0.38			0.63	0.59	0.85	1.11	1.74	3.55
25	0.32	0.26	0.26	0.67	0.63	0.55	0.71	1.23	2.36	3.94
26	0.35	0.31	0.26	0.44	0.60	0.51	0.77	1.27	2.25	3.68
27	0.37	0.20	0.29	0.49	0.55	0.71	0.90	1.08	1.99	3.28
28	0.35	0.22	0.33	0.43	0.63	0.50	1.02	1.18	2.12	3.49
29	0.49	0.20	0.33	0.43	0.60	0.57	0.72	1.18	2.13	3.61

Table 14a: CE-SDS reduced fragments at 5°C, 25°C and 40°C

-50-

Formulation No.	Temp	5°C			25°C			40°C		
	T = 0	4w	13w	26w	4w	8w	13w	2w	4w	8w
1	1.26	1.31	1.10	1.31	1.48	1.51	1.83	2.40	3.65	4.50
21	1.32	1.26	1.14	1.27	1.64	1.44	1.84	2.37	5.45	4.09
22	1.41	1.31	1.06	1.14	2.02	1.49	1.71	2.34	3.37	3.85
23	1.31	1.31	1.03	1.25	1.90	1.48	1.67	2.20	3.05	3.68
24	1.32	1.41			1.50	1.40	1.62	2.24	3.33	3.86
25	1.30	1.34	1.08	1.25	1.77	1.51	1.74	2.31	3.19	3.96
26	1.25	1.34	1.06	1.20	1.54	1.55	1.66	2.28	3.67	3.64
27	1.30	1.40	1.13	1.45	1.56	1.42	1.73	2.21	3.77	3.93
28	1.19	1.62	1.10	1.25	1.58	1.54	1.79	2.24	3.70	4.02
29	1.38	1.35	1.08	1.24	1.79	1.64	1.80	2.55	3.96	5.02

Table 14b: CE-SDS non-reduced fragments at 5°C, 25°C and 40°C**Formulation Study B: Part I Results - Charge Variants**

icIEF main peak degradation rates at 25°C and 40°C are shown in **Table 15**.

- 5 icIEF showed a time- and temperature-dependent decrease in mirikizumab charge variant main peak. This was largely attributable to acidic variant formation. A small (~ <2 %) increase in basic variants was observed after 8 weeks at 40 °C. All formulations performed comparably to Formulation 1. Formulations 1, 25 and 26 comprising sodium chloride appear to provide a benefit of slowing charge variant formation.

-51-

Formulation No.	Buffer	Excipients	pH	Degradation Rate, 40°C (%/week)	R squared, 40°C	Degradation Rate, 25°C (%/week)	R squared, 25°C
1	10 mM citrate	150 mM NaCl	5.5	-3.4663	0.9952	-0.5270	0.9851
21	5 mM citrate	5% w/v mannitol	5.5	-3.9506	0.9996	-0.5156	0.9953
22	5 mM histidine	5% w/v mannitol	5.6	-3.7945	0.9995	-0.5915	0.9551
23	5 mM histidine	5% w/v mannitol	5.9	-4.1399	0.9996	-0.6522	0.9970
24	5 mM histidine	5% w/v mannitol	6.2	-4.1803	1.0000	-0.6558	0.9729
25	10 mM histidine	37.5 mM NaCl 4.1% w/v mannitol	5.5	-3.7592	0.9966	-0.7196	0.9860
26	10 mM histidine	75 mM NaCl 3.3% w/v mannitol	5.5	-3.6310	0.9983	-0.5482	0.9987
27	5 mM histidine	9% w/v sucrose	5.6	-4.1677	0.9952	-0.6874	0.9866
28	5 mM histidine	9% w/v trehalose	5.6	-3.8439	0.9976	-0.6724	0.9742
29	self-buffered	5% w/v mannitol	5.4	-3.7028	0.9962	-0.6380	0.9664

Table 15: icIEF Main Peak Degradation Rates at Elevated Temperature

(The data was fit to a simple linear regression to determine a degradation rate)

Formulation Study B: Part I Results - Subvisible Particles

5 Subvisible particle data revealed that the $\geq 2 \mu\text{m}$ particle counts at 5°C remained at ~ 5000 particles/mL throughout the six months, except for Formulations 23 and 24, both of which exhibited refrigerated solubility issues). Samples stored at 25°C and especially 40°C consistently generated many more particles. Some formulations stored at

-52-

elevated temperatures also showed a trend of increasing particle counts with increasing storage time.

Formulation Study B: Part I Results – Viscosity and Glide Force

5 Viscosity is an important attribute of a drug formulation where the drug product is delivered by an enhanced prefilled syringe (ePFS) or auto-injector (AI) delivery system. As such, viscosities must be low enough to ensure that the AI device can achieve complete delivery of the dose and that, in the case of the ePFS, manual expulsion is not too difficult. The viscosities (at 15°C and 20°C) of the formulations prepared for

10 Formulation Study B - Part I are shown in **Table 16**. The mirikizumab concentration is constant across the samples (~125 mg/mL). Formulations 21-24 and 27-29 have a significantly higher viscosity compared to Formulation 1. Formulations 25 and 26, which contain NaCl and have a lower pH, have a viscosity that is only slightly higher than that of Formulation 1.

15

Formulation No.	Buffer	Excipients	pH	Viscosity (cP)	
				15°C	20°C
1	10 mM citrate	150 mM NaCl	5.5	8.2	6.4
21	5 mM citrate	5% w/v mannitol	5.5	15.4	11.7
22	5 mM histidine	5% w/v mannitol	5.6	15.6	11.9
23	5 mM histidine	5% w/v mannitol	5.9	17.5	13.3
24	5 mM histidine	5% w/v mannitol	6.2	18.1	13.7
25	10 mM histidine	37.5 mM NaCl 4.1% w/v mannitol	5.5	10.4	8.1
26	10 mM histidine	75 mM NaCl 3.3% w/v mannitol	5.5	9.5	7.5
27	5 mM histidine	9% w/v sucrose	5.6	17.2	13.1
28	5 mM histidine	9% w/v trehalose	5.6	18.1	13.7
29	self-buffered	5% w/v mannitol	5.4	14.1	10.9

Table 16: Viscosity

Glide force is another parameter that is helpful in differentiating between formulations. **Figure 2** illustrates that formulations from Formulation Study Part B demonstrate two distinct glide force profiles: those that do not change on accelerated stability and those that do. Removing ionic species such as NaCl from the formulation yields an increase in glide force. This change at accelerated conditions has ultimately manifested at 5°C during long-term storage. This is possibly attributable to a gradual loss of silicone oil on the syringe barrel. Inclusion of ionic species ameliorates this loss of silicone oil and yields formulations that maintain consistent glide forces.

In view of the significantly higher viscosity of Formulations 21-24 and 27-29 and the impact on syringe glide force, replacing the citrate buffer and NaCl excipients to reduce injection site pain has to be balanced with the implications on viscosity and glide force. Accordingly, further formulations were designed and assessed in Formulation Study B: Part II.

15 **Formulation Study B: Part II Results - Purity**

SEC, CE-SDS reduced and CE-SDS non-reduced monomer purity values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Tables 17a-17c**. SEC and both CE-SDS methods showed a time- and temperature-dependent decrease in mirikizumab purity. All test formulations performed comparably to or better than Formulation 1. Formulations 30, 32 and 34 displayed the least decreases in purity at elevated temperatures over the course of the stability study.

-54-

Formulat ion No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	98.49		98.36	98.46	98.25	98.28	98.05	98.04	98.15	97.86	97.22
30	98.43		98.29			98.22	98.07	98.07	98.18	97.93	97.47
31	98.46		98.36	98.48	98.23	98.15	98.03	98.03	98.14	97.72	97.20
32	98.66		98.65	98.78	98.57	98.54	98.41	98.39	98.49	98.13	97.61
33	98.25					97.90			97.87	97.66	
34	98.39		98.62	98.30	98.34	98.23	98.43	98.02	98.21	97.87	97.87
35	98.41	98.19				98.04	97.97	97.86	98.02	97.60	97.22
36	98.37	98.06				97.82	97.70	97.57	97.81	97.44	97.05

Table 17a: SEC Monomer Purity at 5°C, 25°C and 35°C

Formulat ion No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	98.74		98.83	98.80	98.82	98.52	98.20	98.19	98.40	97.79	96.83
30	98.86		98.84			98.64	98.29	98.06	98.49	97.91	97.24
31	99.02		98.92	98.77	98.82	98.49	98.21	98.17	98.51	97.86	97.35
32	98.78		99.13	98.66	98.81	98.47	98.34	98.05	98.48	97.72	97.23
33	98.77					98.42			98.51	97.66	
34	99.12		99.07	98.87	98.55	98.58	98.40	98.28	98.13	97.63	97.23
35	98.62	98.79				98.67	98.36	97.96	98.35	97.76	96.89
36	98.58	98.91				98.42	98.32	98.09	98.13	97.61	97.02

Table 17b: CE-SDS Reduced Monomer Purity at 5°C, 25°C and 35°C

-55-

Formulation No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	98.59		98.37	98.10	98.03	97.81	97.64	97.16	97.17	96.57	95.78
30	98.58		98.26			97.75	97.56	97.26	97.25	96.88	96.42
31	98.51		98.29	98.05	98.00	97.78	97.58	97.01	97.12	96.72	95.65
32	98.44		98.48	98.24	98.15	97.93	97.81	97.28	97.39	96.86	96.20
33	98.24					97.53			96.93	96.55	
34	98.34		98.22	98.43	98.38	97.93	97.23	97.59	97.56	96.86	95.93
35	97.91	98.33				97.94	97.70	96.96	97.62	97.12	95.60
36	97.87	98.09				97.59	97.43	96.51	97.44	96.81	95.43

Table 17c: CE-SDS Non-Reduced Monomer Purity at 5°C, 25°C and 35°C

Formulation Study B: Part II Results - Aggregates

- SEC total aggregates values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Table 18**. SEC showed a time- and temperature-dependent increase in mirikizumab aggregates. All formulations performed comparably to Formulation 1. Formulations 30, 32, and 34 displayed the smallest increases in aggregates over the course of the stability study.

Formulation No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	1.51		1.64	1.54	1.71	1.67	1.89	1.88	1.78	1.98	2.57
30	1.57		1.71			1.73	1.91	1.91	1.78	1.95	2.33
31	1.54		1.64	1.52	1.69	1.68	1.91	1.89	1.79	2.01	2.57
32	1.34		1.35	1.22	1.37	1.34	1.53	1.50	1.43	1.62	2.09
33	1.75					2.04			2.10	2.28	
34	1.59		1.38	1.62	1.60	1.67	1.47	1.86	1.66	1.93	1.82
35	1.50	1.72				1.85	1.99	2.07	1.85	2.21	2.63
36	1.55	1.85				2.12	2.28	2.39	2.17	2.50	2.91

Table 18: SEC Total Aggregates at 5°C, 25°C and 35°C

Formulation Study B: Part II Results - Fragments

CE-SDS Reduced and CE-SDS Non-Reduced fragment values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Tables 19a** and **19b**. Both CE-SDS methods showed a time- and temperature-dependent increase in mirikizumab fragments.

- 5 All formulations performed comparably to or better than Formulation 1.

Formulation No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	0.20		0.31	0.39	0.42	0.59	0.93	0.86	0.79	1.38	2.20
30	0.26		0.18			0.51	0.79	0.84	0.57	1.17	1.59
31	0.19		0.18	0.41	0.43	0.64	0.84	0.89	0.72	1.20	1.78
32	0.29		0.17	0.45	0.49	0.64	0.86	0.97	0.79	1.39	1.93
33	0.35					0.63			0.55	1.19	
34	0.19		0.26	0.45	0.78	0.51	0.80	0.93	0.98	1.39	1.86
35	0.50	0.35				0.50	0.85	0.94	0.92	1.33	2.04
36	0.52	0.31				0.54	0.77	0.78	0.82	1.18	2.05

Table 19a: CE-SDS Reduced Fragments at 5°C, 25°C and 35°C

Formulation No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	1.10		1.19	1.39	1.48	1.63	1.74	2.05	2.05	2.56	3.28
30	1.00		1.17			1.53	1.72	1.82	1.98	2.20	2.58
31	1.11		1.25	1.46	1.47	1.62	1.72	2.14	2.20	2.45	3.38
32	1.27		1.21	1.38	1.48	1.62	1.71	2.14	2.13	2.53	3.10
33	1.18					1.53			2.08	2.20	
34	1.30		1.34	1.22	1.22	1.54	1.84	1.84	1.82	2.43	3.03
35	1.59	1.13				1.38	1.71	2.12	1.71	2.06	3.25
36	1.44	1.16				1.41	1.64	2.07	1.57	1.95	2.96

Table 19b: CE-SDS Non-Reduced Fragments at 5°C, 25°C and 35°C

Formulation Study B: Part II Results - Charge Variants

icIEF charge variant main peak values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Table 20a**. Total acidic variant values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Table 20b**. Total basic variant values for Formulations 1 and 30-36 at 5°C, 25°C and 35°C are shown in **Table 20c**.

icIEF showed a time- and temperature-dependent decrease in mirikizumab charge variant main peak. This was largely attributable to acidic variant formation. A small (~ < 2 %) increase in basic variants was observed after 8 weeks at 35°C. All formulations performed comparably to Formulation 1.

Formulation No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	74.53		76.96	77.54	76.64	74.09	72.90	71.71	72.53	67.30	60.15
30	75.32		76.28			74.10	72.57	71.67	72.20	66.31	58.65
31	74.59		77.08	77.40	76.93	74.20	71.70	72.19	73.94	66.67	60.44
32	75.71		77.65	78.37	77.86	73.90	71.12	71.26	73.12	67.46	60.52
33	74.51					73.55			71.32	65.08	
34	77.29		73.28	76.31	74.13	72.40	71.84	70.92	71.52	64.76	59.85
35	75.77	75.66				74.25	73.62	73.12	71.86	68.53	62.29
36	75.57	75.53				73.93	71.87	71.32	70.91	66.89	59.73

Table 20a: icIEF Main Peak at 5°C, 25°C and 35°C

-58-

Formulat ion No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	22.47		21.39	20.76	21.95	23.12	24.90	25.81	25.08	29.06	36.68
30	21.75		22.13			23.25	25.31	26.09	25.63	30.18	38.93
31	22.47		21.17	20.91	21.55	22.77	25.72	25.17	23.64	28.94	35.97
32	21.61		20.71	20.11	20.57	23.00	25.74	25.80	24.21	28.21	35.66
33	22.58					24.14			26.54	32.28	
34	21.56		23.72	22.20	23.77	24.89	25.37	26.54	25.09	31.90	36.51
35	21.75	22.02				23.04	24.40	24.71	25.08	27.55	34.73
36	21.82	22.18				23.59	26.25	26.77	26.61	29.92	38.10

Table 20b: Total Acidic Variants at 5°C, 25°C and 35°C

Formulat ion No.	Temp	5°C				25°C			35°C		
	T = 0	4w	8w	13w	26w	4w	8w	13w	2w	4w	8w
1	3.01		1.65	1.70	1.42	2.80	2.20	2.47	2.39	3.65	3.17
30	2.93		1.58			2.65	2.12	2.24	2.17	3.51	2.42
31	2.94		1.75	1.69	1.52	3.03	2.59	2.64	2.42	4.40	3.59
32	2.68		1.63	1.52	1.57	3.10	3.14	2.94	2.66	4.33	3.82
33	2.91					2.31			2.13	2.64	
34	1.15		3.00	1.49	2.09	2.71	2.79	2.54	3.39	3.34	3.63
35	2.47	2.33				2.71	1.98	2.17	3.06	3.92	2.98
36	2.61	2.29				2.48	1.88	1.91	2.48	3.19	2.16

Table 20b: Total Basic Variants at 5°C, 25°C and 35°C

5 Formulation Study B: Part II Results - Viscosity

The viscosities (at 15°C and 20°C) of the formulations prepared for Formulation Study B - Part II are shown in **Table 21**. The mirikizumab concentration is roughly constant across the samples (~125 mg/mL). It was observed in Formulation Study B Part I and confirmed in this study that elimination or reduction in the concentration of NaCl

-59-

leads to increased viscosity. The data in **Table 21** illustrates that reduction of the pH can lower viscosity.

Formulation No.	Buffer	Excipients	pH	Viscosity (cP)	
				15°C	20°C
1	10 mM citrate	150 mM NaCl	5.4	8.3	6.5
30	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	5.9	12.6	9.6
31	self-buffered	25 mM NaCl 4.1% w/v mannitol	5.3	11.3	8.6
32	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	5.2	9.9	7.6
33	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	6.3	NT	NT
34	5 mM histidine	25 mM NaCl 4.1% w/v mannitol	5.6	11.1	8.5
35	self-buffered	150 mM NaCl	5.5	7.2	5.8
36	self-buffered	25 mM NaCl 4.1% w/v mannitol	6.0	12.1	9.7

Table 21: Viscosity

5

The data from Formulation Study B Parts I and II was assessed and preferred formulations were designed and assessed in Formulation Study B Part III.

Formulation Study B: Part III Results - Purity

10 SEC, CE-SDS Reduced and CE-SDS Non-Reduced monomer purity values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Tables 22a-22c**. SEC and both CE-SDS methods showed a time- and temperature-dependent decrease in mirikizumab purity. All test formulations performed comparably to or better than Formulation 1.

15

-60-

Formulat ion No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	98.80	98.81	98.83	98.78	98.57	98.49	98.28	98.47	98.18	97.63
37	99.17	99.07	99.07	99.05	98.82	98.72	98.61	98.71	98.44	97.89
38	98.63	98.57	98.57	98.55	98.35	98.27	98.04	98.25	97.96	97.36
39	98.51	98.43	98.34	98.51	98.29	98.16	98.06		97.89	97.44
40	99.31	99.24	99.30	99.19	99.04	98.69	98.64	98.86	98.47	98.05

Table 22a: SEC Monomer Purity at 5°C, 25°C and 35°C

Formulat ion No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	98.79	98.66	98.62	98.92	98.41	98.53	98.14	98.34	97.28	97.19
37	98.46	98.72	98.77	99.07	98.72	98.51	98.13	98.52	98.10	97.52
38	98.90	98.92	98.73	98.80	98.37	98.50	97.94	98.46	98.00	97.50
39	99.10	98.64	98.67	98.98	98.64	98.31	98.21		98.03	97.05
40	98.75	98.82	98.99	98.90	98.71	98.69	97.91	98.30	98.12	97.51

Table 22b: CE-SDS Reduced Monomer Purity at 5°C, 25°C and 35°C

Formulat ion No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	98.12	98.48	97.04	98.22	98.17	97.41	97.12	97.54	97.26	95.59
37	98.24	98.53	98.09	98.27	98.22	97.43	97.25	97.51	97.48	95.80
38	97.86	98.50	98.00	98.09	98.13	97.35	97.02	97.53	97.27	95.40
39	98.39	98.19	98.11	98.36	97.77	97.43	97.04		97.06	96.12
40	98.49	98.29	97.89	98.29	97.84	97.50		97.96	96.94	95.84

Table 22c: CE-SDS Non-Reduced Monomer Purity at 5°C, 25°C and 35°C

-61-

Formulation Study B: Part III Results - Aggregates

SEC total aggregates values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Table 23**. SEC showed a time- and temperature-dependent increase in mirikizumab aggregates. All formulations performed comparably to Formulation 1.

5

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	1.17	1.19	1.17	1.22	1.36	1.46	1.62	1.46	1.69	2.17
37	0.83	0.92	0.93	0.95	1.09	1.19	1.31	1.22	1.46	1.88
38	1.37	1.42	1.40	1.45	1.58	1.66	1.86	1.67	1.92	2.37
39	1.49	1.55	1.60	1.49	1.61	1.76	1.86		1.90	2.33
40	0.69	0.76	0.70	0.81	0.92	1.17	1.20	1.05	1.32	1.80

Table 23: SEC Total Aggregates at 5°C, 25°C and 35°C**Formulation Study B: Part III Results - Fragments**

CE-SDS reduced and CE-SDS non-reduced fragment values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Tables 24a** and **24b**. Both CE-SDS methods showed a time- and temperature-dependent increase in mirikizumab fragments. All formulations performed comparably to or better than Formulation 1.

10

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	0.41	0.57	0.47	0.33	0.74	0.62	0.96	0.76	1.68	1.98
37	0.67	0.57	0.48	0.23	0.51	0.62	0.97	0.63	1.03	1.53
38	0.42	0.40	0.61	0.35	0.69	0.70	0.99	0.70	1.11	1.67
39	0.23	0.50	0.52	0.27	0.53	0.93	1.02		1.15	2.00
40	0.59	0.35	0.26	0.27	0.45	0.44	1.13	0.76	0.94	1.60

Table 24a: CE-SDS Reduced Fragments at 5°C, 25°C and 35°C

15

-62-

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	1.57	1.25	2.58	1.29	1.43	2.01	2.20	1.85	2.11	3.37
37	1.38	1.19	1.51	1.24	1.40	1.93	2.05	1.83	1.95	3.17
38	1.68	1.21	1.53	1.34	1.41	2.00	2.26	1.80	2.12	3.49
39	1.25	1.52	1.61	1.28	1.82	2.11	2.35		2.39	3.11
40	1.24	1.43	1.74	1.31	1.74	1.98		1.59	2.41	3.33

Table 24b: CE-SDS Non-Reduced Fragments at 5°C, 25°C and 35°C**Formulation Study B: Part III Results - Charge Variants**

icIEF charge variant main peak values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Table 25a**. Total acidic variant values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Table 25b**. Total basic variant values for Formulations 1 and 37-40 at 5°C, 25°C and 35°C are shown in **Table 25c**.

icIEF showed a time- and temperature-dependent decrease in mirikizumab charge variant main peak. This was largely attributable to acidic variant formation. A small (~ < 2 %) increase in basic variants was observed after 8 weeks at 35°C. All formulations performed comparably to Formulation 1.

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	77.78	76.89	77.20	77.01	75.35	73.19	72.21	72.62	67.51	60.38
37	78.27	78.72	78.66	79.48	76.72	76.23	74.26	74.36	70.03	63.17
38	77.23	76.57	77.36	77.13	74.34	74.56	71.57	74.53	69.12	62.48
39	78.34	76.03	78.06	78.25	74.08	74.84	71.38		71.43	62.26
40	77.29	78.68	79.40	78.51	77.38	75.52	73.06	71.02	69.74	62.27

Table 25a: icIEF Main Peak at 5°C, 25°C and 35°C

-63-

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	20.71	21.73	21.23	20.57	23.02	24.30	25.17	24.97	30.05	35.84
37	19.33	19.31	19.20	18.01	20.87	20.80	22.58	21.95	27.09	32.66
38	20.63	21.74	21.01	20.66	23.60	22.95	25.72	22.88	28.40	33.63
39	18.11	22.11	19.03	18.13	23.35	21.93	24.34		24.89	33.12
40	19.08	18.44	18.70	18.72	19.89	21.43	23.76	25.92	25.76	33.52

Table 25b: Total Acidic Variants at 5°C, 25°C and 35°C

Formulation No.	Temp	5°C			25°C			35°C		
	T = 0	4w	12w	26w	4w	8w	12w	2w	4w	8w
1	1.51	1.38	1.57	2.42	1.63	2.51	2.62	2.41	2.44	3.78
37	2.40	1.97	2.14	2.52	2.40	2.97	3.15	3.69	2.88	4.18
38	2.14	1.69	1.63	2.21	2.06	2.48	2.71	2.60	2.48	3.88
39	3.55	1.85	2.91	3.62	2.56	3.23	4.28		3.68	4.62
40	3.63	2.88	1.90	2.77	2.73	3.05	3.18	3.06	4.50	4.21

Table 25c: Total Basic Variants at 5°C, 25°C and 35°C

5 Formulation Study B: Conclusions

The purpose of Formulation Study B was to identify a high concentration mirikizumab formulation that may reduce injection pain discomfort that may be associated with formulations comprising NaCl and/or citrate buffer while maintaining the excellent stability characteristics of the preferred formulations identified in Formulation Study Part A. Through the series of studies described above, the preferred formulation comprises (i) mirikizumab, (ii) 5mM of a histidine buffer, (iii) 50 mM of NaCl, (iv) 3.3% w/v of mannitol, and (v) 0.03% w/v of polysorbate 80, wherein the pH of the formulation is 5.5.

The formulations described herein may be evaluated in clinical trials in human patients.

Example 4: Clinical Study - Assessment of mirikizumab formulations in healthy subjects

Overview

The preferred formulation from Formulation Study A (mirikizumab, 10 mM citrate buffer, 150 mM NaCl, 0.05% w/v polysorbate 80, pH 5.5)(hereinafter referred to as Formulation A-P) and the preferred formulation from Formulation Study B (mirikizumab, 5mM of a histidine buffer, 50 mM of NaCl, 3.3% w/v of mannitol, 0.03% w/v of polysorbate 80, pH 5.5)(Formulation B-P) were investigated in clinical trials in human patients to compare relative bioavailability and injection site reaction profiles, in particular, injection site pain profiles.

The study is a Phase 1, subject-blind, investigator-blind, 2-arm, randomized, single dose, parallel design study in healthy subjects. Eligible subjects were admitted to the clinical research unit (CRU) on Day -1 and randomized 1:1 to 1 of 2 possible treatments and, within treatments, 1:1:1 to 3 possible injection locations (arms, thighs, or abdomen) using a computer-generated allocation code. Subjects were allowed to leave the CRU after completing the 4-hour safety assessments on Day 1, at the investigator's discretion, and were to return for pharmacokinetic sampling and safety assessments at predefined outpatient visits up to 12 weeks post dose. Safety and tolerability were assessed from clinical laboratory tests, vital sign measurements, recording of adverse events and physical examination.

Formulation A-P and Formulation B-P were as 1-mL single-dose, pre-filled, disposable manual syringes designed to deliver 100 mg of mirikizumab. The study duration for each participant was up to 16 weeks, which included a 4-week screening period, intervention on Day 1, and 12 week post-dose assessment period with follow-up. On Day 1, subjects received 2×1 -mL PFS subcutaneous (SC) injections into the arms, thighs, or abdomen, according to the randomization schedule.

Objectives

Certain objectives of the study are:

- i) To evaluate the relative bioavailability of a single 200-mg SC dose (2×1 -mL PFS injections) of mirikizumab Formulation B-P compared to the mirikizumab Formulation A-P

-65-

- The endpoints are $C_{\max}$, $AUC(0-\infty)$, and $AUC(0-t_{\text{last}})$ ($AUC(0-\infty)$ = area under the concentration versus time curve from time 0 to infinity; $AUC(0-t_{\text{last}})$ = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; $C_{\max}$ = maximum observed drug concentration).
- ii) To evaluate the safety and tolerability of a single 200-mg SC dose (2×1 -mL PFS injections) of mirikizumab Formulation B-P compared to the mirikizumab Formulation A-P;
- The endpoints are Treatment Emergent Adverse Effects (TEAEs) and Serious Adverse Effects (SAEs).
- iii) To evaluate injection site reactions (ISRs), including pain
- The endpoints are severity, duration and location of erythema, bruising, induration, pain, pruritus, and edema, and the VAS pain score and bleeding immediately after injection.

Methods

20 Subjects were required to be overtly healthy males or females, aged between 18 and 75 years, with a body mass index of 18.0 to 32.0 kg/m², inclusive, at screening. Of the 60 subjects enrolled in the study, 19 were male and 41 were female. The subjects' age ranged from 19 to 74 years.

25 Mirikizumab Formulation A-P and mirikizumab Formulation B-P were supplied as 1-mL single-dose, pre-filled, disposable manual syringes designed to deliver 100 mg of mirikizumab.

On Day 1, subjects received 2×1 -mL PFS SC injections into the arms, thighs, or abdomen.

Subjects randomized to a group with the arm or thigh as the injection area will
30 have:

- (a) the first injection administered to the left limb, and

-66-

- (b) the second injection administered to the corresponding (contra-lateral) right limb.

Subjects randomized to the group with the abdomen as the injection area will have

- (a) the first injection administered to the lower left quadrant, and
5 (b) the second injection administered to the lower right quadrant of the abdomen. The second injection should be administered 20 ($\pm$ 2) minutes after the first injection.

Outpatient visits occurred on Days 3, 5, 8, 11, 15, 22, 29, 43, 57, 71 and 85.

Pharmacokinetic (PK) samples were collected on Days 1 (pre-dose), 3, 5, 8, 11, 15, 22,
10 29, 43, 57, 71 and 85. AE and concomitant medication assessments were performed on Days -1, 1, 3, 5, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 85. Safety assessment telephone calls were performed on Days 36, 50 and 64. Injection site assessments for erythema, induration, pruritus, edema, pain (first injection site only), and bruising were performed at 1, 5, 15, 30, 60, 120 and 240 minutes post-dose on Day 1.

15

Results

(a) Pharmacokinetic analyses

The following PK parameter estimates for mirikizumab were calculated using noncompartmental methods using Phoenix WinNonlin Version 8.1.

-67-

Parameter	Units	Definition
AUC(0-t _{last})	day*µg/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	day*µg/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t _{last} -∞)	%	percentage of AUC(0-∞) extrapolated
C _{max}	µg/mL	maximum observed drug concentration
t _{max}	day	time of maximum observed drug concentration
t _{1/2}	day	half-life associated with the terminal rate constant (λ _z) in non-compartmental analysis
CL/F	L/day	apparent total body clearance of drug calculated after extravascular administration
V _z /F	L	apparent volume of distribution during the terminal phase after extravascular administration
V _{ss} /F	L	apparent volume of distribution at steady state after extravascular administration

Arithmetic mean concentration-time profiles were plotted using nominal time points per the protocol. Mean concentrations were plotted for a given time if 2/3 of the individual data at that time point had quantifiable measurements within the sampling window (± 10%).

Statistical analysis of the PK parameters between mirikizumab Formulation A-P and mirikizumab Formulation B-P. Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) parameters were evaluated in a linear fixed effects model with fixed effects for treatment formulation and injection-site location. The differences between the mirikizumab Formulation A-P and mirikizumab Formulation B-P were back-transformed to present the ratios of geometric LS means and the corresponding 90% CI. Parameters were summarized by treatment formulation.

The summary PK parameters for mirikizumab Formulation A-P and mirikizumab Formulation B-P are shown in **Table 26**.

Parameter	Geometric mean (Geometric CV%) [n]	
	Formulation A-P (N=30)	Formulation B-P (N=30)
AUC(0-t _{last}) (ug.day/mL)	225 (56%) [30]	206 (46%) [30]
AUC(0-∞) (ug.day/mL)	229 (56%) [30]	209 (45%) [30]
%AUC(t _{last} -∞) (%)	1.52 (59%) [30]	1.59 (61%) [30]
C _{max} (ug/mL)	12.7 (48%) [30]	11.6 (45%) [30]
t _{max} (day)#	4.00 (4.00-7.00) [30]	4.00 (2.00-10.00) [30]
t _{1/2} (day)*	11.5 (6.56-18.7) [30]	11.8 (7.53-17.4) [30]
CL/F (L/day)	0.874 (56%) [30]	0.955 (45%) [30]
V _z /F (L)	14.5 (40%) [30]	16.3 (43%) [30]
V _{ss} /F (L)	15.4 (44%) [30]	17.1 (47%) [30]

Table 26: Summary of the Pharmacokinetic Parameters of Mirikizumab

Abbreviations: %AUC(t_{last}-∞) = percentage of AUC(0-∞) extrapolated; AUC(0-

∞) = area under the concentration versus time curve from time zero to infinity;

AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration;

CL/F = apparent total body clearance calculated after extravascular administration;

C_{max} = maximum observed drug concentration;

CV = coefficient of variation;

N = number of subjects;

n = number of observations;

t_{1/2} = half-life associated with the terminal rate constant in noncompartmental analysis;

t_{max} = time of maximum observed drug concentration;

V_{ss}/F = apparent volume of distribution at steady state after extravascular administration;

V_z/F = apparent volume of distribution during the terminal phase after extravascular administration

Median (minimum-maximum)

* Geometric mean (minimum-maximum)

Formulation A-P = 200 mg Mirikizumab Formulation (100 mg/mL) 2 x 1 mL PFS;

Formulation B-P = 200 mg Mirikizumab Formulation (100 mg/mL) 2 x 1 mL PFS

-69-

Overall, no statistically significant differences in C_{max}, AUC(0-∞), and AUC(0-t_{last}) were observed following administration of the mirikizumab Formulation A-P and mirikizumab Formulation B-P, with the 90% CIs for the ratios of geometric LS means including unity (**Table 27**).

Parameter	Treatment	n	Geometric least squares mean	Ratio of geometric least squares mean (Formulation B-P: Formulation A-P)	90% CI for the ratio (Lower, Upper)
AUC(0-t _{last}) (ug.day/mL)	Formulation A-P	30	225		
	Formulation B-P	30	206	0.915	(0.760, 1.10)
AUC(0-∞) (ug.day/mL)	Formulation A-P	30	229		
	Formulation B-P	30	209	0.915	(0.761, 1.10)
C _{max} (ug/mL)	Formulation A-P	30	12.7		
	Formulation B-P	30	11.6	0.907	(0.775, 1.06)

5 **Table 27: Statistical Analysis of the Pharmacokinetic Parameters of Mirikizumab**

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity;
AUC(0-t_{last}) = area under the concentration versus time curve from time zero to time t, where t is the last
time point with a measurable concentration;

CI = confidence interval;

10 C_{max} = maximum observed drug concentration;

n = number of observations

Formulation A-P = 200 mg Mirikizumab Formulation (100 mg/mL) 2 x 1 mL PFS;

Formulation B-P = 200 mg Mirikizumab Formulation (100 mg/mL) 2 x 1 mL PFS Model: Log(PK) =

Treatment + Location + Random Error

15

There was no statistically significant difference in the median t_{max} of
mirikizumab between the formulations. Serum concentrations of mirikizumab declined
after t_{max}, and the resulting geometric mean t_{1/2} values following dosing with the

-70-

mirikizumab Formulation A-P and mirikizumab Formulation B-P were similar, being 11.5 days (276 hours) and 11.8 days (283 hours), respectively. Between subject variability (CV%) estimates for AUC(0-tlast), AUC(0 ∞), and Cmax were moderate to high 48% to 56% for the mirikizumab Formulation A-P, and 45% to 46% for the mirikizumab Formulation B-P.

(b) Safety analyses

TEAEs

The incidence of all TEAEs reported during the study was similar between subjects who received mirikizumab Formulation A-P and mirikizumab Formulation B-P (**Table 28**). Injection site data was prospectively assessed, with any event relating to an injection site captured as a study endpoint related to ISRs and not recorded as an AE unless that event qualified as an SAE.

	Number of Subjects with Events (Percentage of Subjects with Events)	
	200 mg Mirikizumab Formulation A-P (N = 30)	200 mg Mirikizumab Formulation B-P (N = 30)
All TEAEs	3 (10.0%)	3 (10.0%)
Mild	2 (6.7%)	5 (16.7%)
Moderate	3 (10.0%)	2 (6.7%)
Severe	0	0
Treatment-related AEs	2 (6.7%)	1 (3.3%)
Fatal AEs	0	0
SAEs	0	0
AEs leading to discontinuation from study	0	0
Infections	0	1 (3.3%)
Systemic Allergic/Hypersensitivity Reactions	0	0
ISRs	23 (76.7%)	15 (50.0%)

Table 28: Summary of Adverse Events

Overall, 3 (10.0%) subjects who received mirikizumab Formulation A-P reported a total of 5 TEAEs and 3 (10.0%) subjects who received mirikizumab Formulation B-P reported a total of 7 TEAEs (**Tables 29a** and **29b**). TEAEs that were considered related to mirikizumab were reported as follows:

-71-

- a) Mirikizumab Formulation A-P (4 events in 2 [6.7%] subjects)
- 1 subject had single events of mild nausea, moderate vomiting, and moderate headache
 - 1 subject had a single event of mild nausea
- b) Mirikizumab Formulation B-P (2 events in 1 subject [3.3%])
- 1 subject had single events of mild nausea and mild headache

10

All but one TEAE of a moderate broken heel bone, considered related to other medical condition, had resolved by the end of the study, and the majority resolved without treatment. Two treatment-related TEAEs of headache required paracetamol, and the broken heel bone, required apixaban, hydrocodone, and paracetamol.

Treatment	All causalities		Related to study treatment	
	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*
Formulation A-P (Arm) (N=10)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)
Formulation A-P (Thigh) (N=10)	2 [20.0%]	Mild (2) Moderate (2) Severe (0) Total (4)	2 [20.0%]	Mild (2) Moderate (2) Severe (0) Total (4)
Formulation A-P (Abdomen) (N=10)	1 [10.0%]	Mild (0) Moderate (1) Severe (0) Total (1)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)

-72-

Treatment	All causalities		Related to study treatment	
	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*

* Only the maximum severity of each adverse event is reported

Table 29a: Summary of Treatment-Emergent Adverse Events for Formulation A-P

Treatment	All causalities		Related to study treatment	
	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*	Number of subjects [%] with treatment-emergent adverse events	Number of treatment-emergent adverse events and severity*
Formulation B-P (Arm) (N=10)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)
Formulation B-P (Thigh) (N=10)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)	0 [0.0%]	Mild (0) Moderate (0) Severe (0) Total (0)
Formulation B-P (Abdomen) (N=10)	3 [30.0%]	Mild (5) Moderate (2) Severe (0) Total (7)	1 [10.0%]	Mild (2) Moderate (0) Severe (0) Total (2)

* Only the maximum severity of each adverse event is reported

Table 29b: Summary of Treatment-Emergent Adverse Events for Formulation B-P

Deaths, SAEs and discontinuations

No deaths occurred during the study. No SAEs occurred during the study. There were no discontinuations due to AEs during the study.

5 Injection site assessments

Injection-site bleeding was reported in 3 (10.0%) subjects who received mirikizumab Formulation A-P (2 arm, 1 abdomen) and 3 (10.0%) subjects who received mirikizumab Formulation B-P (2 arm, 1 thigh).

10 The first injection site for each subject was assessed prospectively for ISRs at the time points indicated above. The injection site was assessed for erythema, edema, induration, pruritus, and pain, with each positive response in any category at each time point counted as an event. In addition, any spontaneously reported ISR at either the first or second injection site was assessed as above.

15 Injection site reaction data are summarized in **Tables 30a** and **30b**. This includes data from the planned prospective assessments and assessment of ISRs spontaneously reported at each injection site on Day 9 by 1 subject who received Formulation A-P (arm).

-74-

Parameter		Formulation A-P (Arm) (N=10)	Formulation A-P (Thigh) (N=10)	Formulation A-P (Abdomen) (N=10)
Number (%) of subjects reporting ISRs		7 (70.0%)	8 (80.0%)	8 (80.0%)
Number of reported ISRs		19	14	14
Time of ISR relative to study drug administration*	During administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Within 30 minutes of administration	13 (68.4%)	12 (85.7%)	13 (92.9%)
	>30 minutes and up to 6 hours after administration	0 (0.0%)	2 (14.3%)	1 (7.1%)
	>6 hours and up to 24 hours after administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>24 hours and up to 14 days after administration	6 (31.6%)	0 (0.0%)	0 (0.0%)
	>14 days after administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)
Size of erythema*	Barely Noticeable (less than 25 mm diameter)	6 (31.6%)	5 (35.7%)	4 (28.6%)
	Slight (25 - 50 mm diameter)	2 (10.5%)	0 (0.0%)	0 (0.0%)
	Moderate (51 - 100 mm diameter)	1 (5.3%)	0 (0.0%)	0 (0.0%)
	Severe (more than 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity of erythema*	Noticeable but very mild redness	6 (31.6%)	5 (35.7%)	4 (28.6%)
	Clearly red	3 (15.8%)	0 (0.0%)	0 (0.0%)
	Bright red	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Dark with ulceration, or necrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)

Parameter		Formulation A-P (Arm) (N=10)	Formulation A-P (Thigh) (N=10)	Formulation A-P (Abdomen) (N=10)
Severity of induration*	Barely Noticeable (less than 25 mm diameter)	2 (10.5%)	0 (0.0%)	0 (0.0%)
	Slight (25 - 50 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (51 - 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe (more than 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did the subject have injection site pain?*	Yes	6 (31.6%)	9 (64.3%)	10 (71.4%)
	No	13 (68.4%)	5 (35.7%)	4 (28.6%)
Severity of pruritus*	Mild	2 (10.5%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity of edema*	Mild (less than 2 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (2-5 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe (more than 5 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Percentages are based on number of reported ISRs

Subjects with a change in severity in ISRs are only counted one time at the highest severity

Table 30a: Summary of Injection Site Reaction Data for Formulation A-P

-76-

Parameter		Formulation B-P (Arm) (N=10)	Formulation B-P (Thigh) (N=10)	Formulation B-P (Abdomen) (N=10)
Number (%) of subjects with ISRs		6 (60.0%)	4 (40.0%)	5 (50.0%)
Number of ISRs		7	6	7
Time of ISR relative to study drug administration*	During administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Within 30 minutes of administration	5 (71.4%)	5 (83.3%)	7 (100.0%)
	>30 minutes and up to 6 hours after administration	2 (28.6%)	1 (16.7%)	0 (0.0%)
	>6 hours and up to 24 hours after administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>24 hours and up to 14 days after administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
	>14 days after administration	0 (0.0%)	0 (0.0%)	0 (0.0%)
Size of erythema*	Barely Noticeable (less than 25 mm diameter)	3 (42.9%)	3 (50.0%)	1 (14.3%)
	Slight (25 - 50 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (51 - 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe (more than 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity of erythema*	Noticeable but very mild redness	3 (42.9%)	3 (50.0%)	1 (14.3%)
	Clearly red	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Bright red	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Dark with ulceration	0 (0.0%)	0 (0.0%)	0 (0.0%)

-77-

Parameter		Formulation B-P (Arm) (N=10)	Formulation B-P (Thigh) (N=10)	Formulation B-P (Abdomen) (N=10)
Severity of induration*	Barely Noticeable (less than 25 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Slight (25 - 50 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (51 - 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe (more than 100 mm diameter)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Did the subject have injection site pain?*	Yes	4 (57.1%)	3 (50.0%)	6 (85.7%)
	No	3 (42.9%)	3 (50.0%)	1 (14.3%)
Severity of pruritus*	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severity of edema*	Mild (less than 2 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate (2-5 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe (more than 5 mm)	0 (0.0%)	0 (0.0%)	0 (0.0%)

* Percentages are based on number of reported ISRs

Subjects with a change in severity in ISRs are only counted one time at the highest severity

Table 30b: Summary of Injection Site Reaction Data for Formulation B-P

5 Overall, 23 (76.7%) subjects who received the mirikizumab Formulation A-P (7 arm, 8 thigh, 8 abdomen) reported 47 ISRs, and 15 (50.0%) subjects who received the mirikizumab Formulation B-P (6 arm, 6 thigh, 6 abdomen) reported 20 ISRs. The number of ISRs were similar between injection sites (arm, thigh, abdomen) for subjects who received the mirikizumab Formulation A-P or mirikizumab Formulation B-P. The

-78-

majority of reports of ISRs consisted of mild reaction. Most responses (82.1%) were made within 30 minutes of treatment administration.

Categorical Pain

- 5 During assessment of ISRs, subjects were asked whether there was injection site pain (“yes/no”). Following administration of mirikizumab Formulation A-P, 25 events of pain were reported by 22 (73.3%) subjects (6 arm, 8 thigh, 8 abdomen). Following administration of mirikizumab Formulation B-P, 13 events of pain were reported by 11 (36.7%) subjects (4 arm, 3 thigh, 4 abdomen).

10

Pain Visual Analog Scale

Reports of injection-site pain were further assessed using the VAS pain assessment. A summary of VAS pain score data by injection site is shown in **Tables 31a** and **31b**.

Treatment		Pain at this time* (mm)			
		1 minute	5 minutes	15 minutes	30 minutes
Formulation A-P (Arm) (N=10)	Mean	19.7	5.0	0.8	NC
	SD	17.9	7.0	1.3	NC
	Median	16.0	1.5	0.0	NC
	Minimum	2	0	0	0
	Maximum	59	18	4	0
	n	10	10	10	1
Formulation A-P (Thigh) (N=10)	Mean	36.9	7.9	3.5	NC
	SD	25.6	16.0	6.8	NC
	Median	28.0	0.5	1.0	NC
	Minimum	6	0	0	0
	Maximum	84	51	22	1
	n	10	10	10	2
Formulation A-P (Abdomen) (N=10)	Mean	21.6	5.1	0.6	NC
	SD	19.1	11.3	1.0	NC
	Median	17.0	1.5	0.0	NC
	Minimum	2	0	0	0
	Maximum	56	37	2	0
	n	10	10	10	1

-79-

Treatment		Pain at this time* (mm)			
		1 minute	5 minutes	15 minutes	30 minutes
Formulation A-P (Overall)(N=30)	Mean	26.1	6.0	1.6	0.3
	SD	21.8	11.7	4.1	0.5
	Median	22.5	1.0	0.0	0.0
	Minimum	2	0	0	0
	Maximum	84	51	22	1
	n	30	30	30	4

NC = Not calculated

*0 mm = No pain and 100 mm = Worst imaginable pain

At time points 30, 60, 120, and 240 minutes, VAS pain assessment occurred only if pain was reported as "yes" on the Injection-site Assessment form.

Table 31a: Summary of the VAS Pain Score Data for Formulation A-P

Treatment		Pain at this time* (mm)			
		1 minute	5 minutes	15 minutes	30 minutes
Formulation B-P (Arm) (N=10)	Mean	14.0	1.4	0.5	NC
	SD	14.0	2.3	1.0	NC
	Median	10.5	0.0	0.0	NC
	Minimum	0	0	0	0
	Maximum	44	6	3	0
	n	10	10	10	1
Formulation B-P (Thigh) (N=10)	Mean	13.1	1.3	0.9	
	SD	10.1	1.9	1.6	
	Median	11.0	1.0	0.0	
	Minimum	3	0	0	
	Maximum	36	6	5	
	n	10	10	10	
Formulation B-P (Abdomen) (N=10)	Mean	10.8	3.1	1.7	NC
	SD	7.1	2.7	2.0	NC
	Median	9.5	2.5	1.0	NC
	Minimum	0	0	0	0
	Maximum	26	9	5	0
	n	10	10	10	1
Formulation B-P (Overall)(N=30)	Mean	12.6	1.9	1.0	NC
	SD	10.5	2.4	1.6	NC
	Median	10.0	1.0	0.0	NC
	Minimum	0	0	0	0
	Maximum	44	9	5	0
	n	30	30	30	2

NC = Not calculated
*0 mm = No pain and 100 mm = Worst imaginable pain
At time points 30, 60, 120, and 240 minutes, VAS pain assessment occurred only if pain was reported as “yes” on the Injection-site Assessment form.

Table 31b: Summary of the VAS Pain Score Data for Formulation B-P

Within 1 minute post-dose, mean VAS pain score was 26.1 following administration of mirikizumab Formulation A-P, and 12.6 following administration of mirikizumab Formulation B-P. This difference is statistically significant, with the 90% CIs of the difference in geometric LS means excluding unity (**Table 32**).

Treatment	n	Least squares mean	Difference of least squares mean (Formulation B-P – Formulation A-P)	90% CI for the difference (Lower, Upper)
Formulation A-P (Overall)	30	26.07		
Formulation B-P (Overall)	30	12.63	-13.43	(-20.75, -6.12)
Formulation A-P (Arm)	10	19.70		
Formulation B-P (Arm)	10	14.00	-5.70	(-18.16, 6.76)
Formulation A-P (Thigh)	10	36.90		
Formulation B-P (Thigh)	10	13.10	-23.80	(-38.90, -8.70)
Formulation A-P (Abdomen)	10	21.60		
Formulation B-P (Abdomen)	10	10.80	-10.80	(-21.95, 0.35)

Abbreviations: CI = confidence interval; n = number of observations
The VAS scores range from 0 mm (no pain) to 100 mm (worst imaginable pain)

Table 32: Statistical Analysis of 1-Minute Pain Measurement using VAS Data

At 5 minute post-dose, mean VAS pain score was 6.0 following administration of mirikizumab Formulation A-P, and 1.9 following administration of mirikizumab Formulation B-P.

Similar findings were observed when the thigh injection site was considered separately, although there was no statistically significant difference in mean VAS pain

-81-

score between the mirikizumab Formulation A-P and mirikizumab Formulation B-P at the arm and abdomen injection sites. The majority of pain reported was mild in severity. Severe pain was only reported by 2 subjects who received the mirikizumab Formulation A-P (thigh).

-82-

Listing of Sequences**Heavy Chain CDRs**

SEQ ID NO: 1 GYKFTRYVMH
5 SEQ ID NO: 2 YINPYNDGTNYNEKFKG
SEQ ID NO: 3 ARNWD TGL

Light Chain CDRs

SEQ ID NO: 4 KASDHILKFLT
10 SEQ ID NO: 5 GATSLET
SEQ ID NO: 6 QMYWSTPFT

Heavy Chain Variable Regions

15 SEQ ID NO: 7
QVQLVQSGAEVKKPGSSVKV SCKASGYKFTRYVMHWVRQAPGQGLEWMGYIN
PYNDGTNYNEKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARNWD TGLW
GQGTTVTVSS

20 **Light Chain Variable Regions**

SEQ ID NO: 8
DIQMTQSPSSLSASVGDRVTITCKASDHILKFLTWYQQKPGKAPKLLIYGATSLET
GVPSRFSGSGSGTDFLTISLQPEDFATYYCQMYWSTPFTFGGGTKVEIK
25

Complete Heavy Chain

SEQ ID NO: 9
QVQLVQSGAEVKKPGSSVKV SCKASGYKFTRYVMHWVRQAPGQGLEWMGYIN
30 PYNDGTNYNEKFKGRVTITADKSTSTAYMELSSLRSED TAVYYCARNWD TGLW
GQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA
LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNV D HKPSNTKVDKRVES

-83-

KYGPPCPPCAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL
PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
5 KSLSLSLG

Complete Light Chain

SEQ ID NO: 10

10 DIQMTQSPSSLSASVGDRVTITCKASDHILKFLTWYQQKPGKAPKLLIYGATSLET
GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQMYWSTPFTFGGGTKVEIKRTVAA
PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

CLAIMS:

1. A pharmaceutical formulation comprising:
 - (i) 50 mg/mL – 150 mg/mL of an IL-23p19 antibody;
 - 5 (ii) 8 mM – 12 mM of a citrate buffer;
 - (iii) 100 - 200 mM of sodium chloride (NaCl); and
 - (iv) 0.01% w/v to 0.05% w/v of a surfactant,wherein the pH of the formulation is between 5.0 to 6.0, and
wherein the anti-IL-23p19 antibody comprises a light chain variable region
10 (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the
LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.
2. A pharmaceutical formulation according to claim 1, wherein the anti-IL-23p19
antibody comprises a light chain (LC) and a heavy chain (HC), wherein the amino acid
15 sequence of the LC is SEQ ID NO: 10 and the amino acid sequence of the HC is SEQ ID
NO: 9.
3. A pharmaceutical formulation according to claim 1 or claim 2, wherein the anti-
IL-23p19 antibody is mirikizumab.
20
4. A pharmaceutical formulation according to any one of claims 1-3, wherein the
concentration of the anti-IL-23p19 antibody is about 75 mg/mL to about 150 mg/mL.
5. A pharmaceutical formulation according to any one of claims 1-4, wherein the
25 concentration of the anti-IL-23p19 antibody is about 100 mg/mL to about 150 mg/mL.
6. A pharmaceutical formulation according to any one of claims 1-5, wherein the
concentration of the anti-IL-23p19 antibody is about 100 mg/mL.
- 30 7. A pharmaceutical formulation according to any one of claims 1-5, wherein the
concentration of the anti-IL-23p19 antibody is about 125 mg/mL.

-85-

8. A pharmaceutical composition according to any preceding claim, wherein the concentration of the citrate buffer is about 10 mM.
9. A pharmaceutical formulation according to any preceding claim, wherein the citrate buffer is a sodium citrate buffer.
10. A pharmaceutical formulation according to any preceding claim, wherein the surfactant is polysorbate 20 or polysorbate 80.
11. A pharmaceutical formulation according to claim 10, wherein the surfactant is polysorbate 80.
12. A pharmaceutical formulation according to any one of claims 1-11, wherein the concentration of the surfactant is about 0.03% (w/v).
13. A pharmaceutical formulation according to any one of claims 1-12, wherein the concentration of NaCl is about 150 mM.
14. A pharmaceutical formulation according to any one of claims 1-13, wherein the pH of the formulation is about 5.5.
15. A pharmaceutical formulation according to claim 3, wherein the formulation comprises:
- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
 - (ii) 10 mM of sodium citrate buffer;
 - (iii) 150 mM of NaCl; and
 - (iv) 0.03% w/v of polysorbate 80,
- wherein the pH of the formulation is about 5.5.
16. A pharmaceutical formulation according to claim 15, wherein the formulation comprises 100 mg/mL of mirikizumab.

-86-

17. A pharmaceutical formulation according to claim 15, wherein the formulation comprises 125 mg/mL of mirikizumab.
18. A pharmaceutical formulation comprising:
- 5 (i) 50 mg/mL – 150 mg/mL of an antibody IL-23p19 antibody;
- (ii) 3mM - 12mM of a histidine buffer;
- (iii) 25 - 75 mM of NaCl;
- (iv) 2-5% w/v of a tonicity agent; and
- (iv) 0.01% w/v to 0.05% w/v of a surfactant,
- 10 wherein the pH of the formulation is between 5.0 to 6.0, and
- wherein the anti-IL-23p19 antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.
- 15 19. A pharmaceutical formulation according to claim 18, wherein the anti-IL-23p19 antibody comprises a light chain (LC) and a heavy chain (HC), wherein the amino acid sequence of the LC is SEQ ID NO: 10 and the amino acid sequence of the heavy chain is SEQ ID NO: 9.
- 20 20. A pharmaceutical formulation according to claim 18 or claim 19, wherein the anti-IL-23p19 antibody is mirikizumab.
21. A pharmaceutical formulation according to any one of claims 18-20, wherein the concentration of the anti-IL-23p19 antibody is about 75 mg/mL to about 150 mg/mL.
- 25 22. A pharmaceutical formulation according to any one of claims 18-21, wherein the concentration of the anti-IL-23p19 antibody is about 100 mg/mL to about 150 mg/mL.
23. A pharmaceutical formulation according to any one of claims 18-22, wherein the
- 30 concentration of the anti-IL-23p19 antibody is about 100 mg/mL.

-87-

24. A pharmaceutical formulation according to any one of claims 18-22 wherein the concentration of the anti-IL-23p19 antibody is about 125 mg/mL.
25. A pharmaceutical composition according to any one of claims 18-23, wherein the concentration of the histidine buffer is about 5 mM.
26. A pharmaceutical composition according to any one of claims 18-25, wherein the tonicity agent is mannitol.
27. A pharmaceutical composition according to claim 26, wherein the concentration of mannitol is 3.3% w/v.
28. A pharmaceutical formulation according to any one of claims 18-27, wherein the surfactant is polysorbate 20 or polysorbate 80.
29. A pharmaceutical formulation according to claim 28, wherein the surfactant is polysorbate 80.
30. A pharmaceutical formulation according to any one of claims 18-29, wherein the concentration of the surfactant is about 0.03% (w/v).
31. A pharmaceutical formulation according to any one of claims 18-30, wherein the concentration of NaCl is about 50 mM.
32. A pharmaceutical formulation according to any one of claims 18-31, wherein the pH of the formulation is about 5.5.
33. A pharmaceutical formulation according to claim 20 comprising:
- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
 - (ii) 5 mM of a histidine buffer;
 - (iii) 50 mM of NaCl;
 - (iv) 3.3% w/v of mannitol; and

-88-

(v) 0.03% w/v of polysorbate 80,
wherein the pH of the formulation is 5.5.

34. A pharmaceutical formulation according to claim 32, wherein the formulation
5 comprises 100 mg/mL of mirikizumab.

35. A pharmaceutical formulation according to claim 32, wherein the formulation
comprises 125 mg/mL of mirikizumab.

10 36. A method of treating and/or preventing psoriasis, ulcerative colitis, Crohn's
Disease, psoriatic arthritis and/or ankylosing spondylitis, wherein the method comprises
administering to a patient a therapeutically effective amount of a pharmaceutical
formulation of any one of claims 1-35.

15 37. A pharmaceutical formulation according to any one of claims 1-35 for use in the
treatment and/or prevention of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic
arthritis and/or ankylosing spondylitis.

20 38. Use of a pharmaceutical formulation according to any one of claims 1-35 in the
manufacture of a medicament for use in the treatment of psoriasis, ulcerative colitis,
Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

39. A method of reducing injection-associated pain experienced by a patient at the
time of, or shortly after, SC, IP and/or IM administration of a pharmaceutical formulation
25 comprising an anti-IL-23p19 antibody, the method comprising administering to a patient
a pharmaceutical formulation according to any one of claims 18-35, wherein, said step of
administering provides a therapeutically favorable level of injection-associated pain.

40. A method of reducing injection-associated pain according to claim 39, wherein the
30 therapeutically favorable level of injection-associated pain comprises a VAS score of less
than 30 mm or less than 20 mm.

-89-

41. An improved method for SC administration of an anti-IL-23p19 antibody to a patient in need thereof, wherein the improvement comprises a reduction in injection-associated pain upon SC administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical
5 formulation according to any of claims 18-35, wherein said step of administering provides an improved level of injection-associated pain and/or provides a therapeutically favorable level of injection-associated pain.
42. An improved method for SC administration of an anti-IL-23p19 antibody
10 according to claim 41, wherein the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.
43. An improved method of treating at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis, wherein the improvement
15 comprises a reduction in injection-associated pain upon the SC administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical formulation according to any one of claims 18-35, wherein said step of administering provides an improved level of injection-associated pain and/or provides a therapeutically favorable level of injection-associated
20 pain.
44. An improved method of treating at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis according to claim 43, wherein the therapeutically favorable level of injection-associated pain comprises a VAS
25 score of less than 30 mm or less than 20 mm.