

Compositions of thymic stromal lymphopoietin (TSLP) binding fragments and methods of use thereof

Field

The present disclosure relates to pharmaceutical compositions comprising antigen binding fragments
5 specific for thymic stromal lymphopoietin (TSLP) suitable for inhalation, as well as a process for preparing
a pharmaceutical composition for inhalation comprising said antigen binding fragment specific for TSLP.
The present disclosure further relates to methods of treating TSLP-related conditions, such as asthma
and COPD, using the pharmaceutical compositions. The pharmaceutical compositions include a mixture
of leucine, trileucine, and histidine that results in a formulation that is suitable for delivering antigen
10 binding fragments derived from anti-TSLP antibodies via inhalation.

Background

Asthma affects an estimated 300 million people worldwide, including all age groups, and poses a serious
burden on the health care system, and on society, through loss of productivity at the workplace and
15 disruption to the family. ("Pocket Guide for Asthma Management and Prevention," Global Initiative for
Asthma; 2019). Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and
cough that vary over time with their occurrence, frequency and intensity. Symptoms are often associated
with bronchoconstriction, airway wall thickening and increased production of mucus. Asthma can have
varying degrees of symptoms and be well controlled, or poorly controlled, based on number of attacks
20 and severity.

Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine produced in response to
environmental and pro-inflammatory stimuli, leads to the activation of multiple inflammatory cells and
downstream pathways. TSLP is increased in the airways of patients with asthma and correlates with Th2
cytokine and chemokine expression. and disease severity. While TSLP is central to the regulation of Th2
25 immunity, it may also play a key role in other pathways of inflammation and therefore be relevant to
multiple asthma phenotypes.

Dry powder formulations comprising anti-TSLP antibody fragments suitable for inhalation for the
treatment of asthma have been described in WO 2021/083908. An anti-TSLP Fab with improved stability
is described in WO 2022/223514. WO2017/042701 and WO 2021/152488 describe methods for treating
30 inflammatory or obstructive airway diseases, such as asthma, using an anti-TSLP antibody or an anti-
TSLP antibody fragment.

There remains a need for further compositions suitable for delivery of antibodies to TSLP via inhalation.
The present invention has been devised in light of the above considerations.

Summary

The present disclosure provides a novel pharmaceutical composition comprising an antibody fragment of an anti-TSLP antibody with notable beneficial characteristics, including high manufacturing yield, low levels of sub-visible particles and minimal throat and device powder retention. A preclinical toxicity study further demonstrated that the novel composition exhibited a favourable toxicity profile, with minimal immune-related toxicity. Hence the described pharmaceutical composition is expected to be safe and achieve clinical benefit when administered to patients for the treatment of TSLP-related conditions.

In a first aspect, the present disclosure provides a pharmaceutical composition comprising spray-dried particles, the spray-dried particles comprising:

- a. about 5% (w/w) to about 15% (w/w) leucine;
- b. about 1% (w/w) to about 5% (w/w) trileucine;
- c. about 1% (w/w) to about 10% (w/w) histidine buffer at a pH of between about pH 5 to pH 6;
- d. about 1% (w/w) to about 80% (w/w) of an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody; and
- e. a glass stabilisation agent.

In some instances, the pharmaceutical composition comprises about 1% (w/w) to about 3% (w/w) trileucine.

In some instances, the pharmaceutical composition comprises about 2% (w/w) trileucine.

In some instances, the pharmaceutical composition comprises about 8% (w/w) to about 12% (w/w) leucine.

In some instances, the pharmaceutical composition comprises about 10.5% (w/w) leucine.

In some instances, the pharmaceutical composition comprises about 1% (w/w) to about 5% (w/w) histidine buffer.

In some instances, the pharmaceutical composition comprises about 2.5% (w/w) to about 3.5% (w/w) histidine buffer.

In some instances, the pharmaceutical composition comprises about 3.14% (w/w) histidine buffer.

In some instances, the pharmaceutical composition comprises about 0.55% (w/w) L-histidine and about 2.59% (w/w) histidine HCl.

In some instances, the antigen binding fragment is present at a concentration of about 1% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 2% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 3% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 10% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 30% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 40% (w/w).

In some instances, the antigen binding fragment is present at a concentration of about 80% (w/w).

In some instances, the total mass solids content of the pharmaceutical composition is 20 mg, and the pharmaceutical composition comprises 0.2 mg, 0.4 mg, 0.6 mg, 2 mg, 6 mg, 8 mg or 16 mg of antigen binding fragment. In such instance, the pharmaceutical composition may comprise 0.4 mg, 2 mg or 8 mg of antigen binding fragment.

5 In some instances, the antigen binding fragment comprises:

- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
- b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
- c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
- d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
- 10 e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
- f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.

In some instances, the antigen binding fragment comprises:

- a. a HCDR1 having the amino acid sequence of SEQ ID NO: 1;
- b. a HCDR2 having the amino acid sequence of SEQ ID NO: 2;
- 15 c. a HCDR3 having the amino acid sequence of SEQ ID NO: 3;
- d. a LCDR1 having the amino acid sequence of SEQ ID NO: 5;
- e. a LCDR2 having the amino acid sequence of SEQ ID NO: 6; and
- f. a LCDR3 having the amino acid sequence of SEQ ID NO: 7.

In some instances, the antigen binding fragment comprises:

- 20 a. a HCDR1 consisting of the amino acid sequence of SEQ ID NO: 1;
- b. a HCDR2 consisting of the amino acid sequence of SEQ ID NO: 2;
- c. a HCDR3 consisting of the amino acid sequence of SEQ ID NO: 3;
- d. a LCDR1 consisting of the amino acid sequence of SEQ ID NO: 5;
- e. a LCDR2 consisting of the amino acid sequence of SEQ ID NO: 6; and
- 25 f. a LCDR3 consisting of the amino acid sequence of SEQ ID NO: 7.

In some instances, the antigen binding fragment comprises a VH domain comprising a sequence at least 95%, 90%, 85% or 80% identical to, SEQ ID NO:4 and a VL domain comprising a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO:8.

30 In some instances, the antigen binding fragment comprises a VH domain comprising the sequence of SEQ ID NO: 4; and a VL domain comprising the sequence of SEQ ID NO: 8.

In some instances, the antigen binding fragment is a Fab, Fab', F(ab')₂, scFv, minibody or diabody.

In some instances, the antigen binding fragment is a Fab.

In some instances, the Fab is of an IgG1 antibody.

35 In some instances, the antigen binding fragment comprises a first sub-unit having the sequence set forth in SEQ ID NO: 28 and a second sub-unit having the sequence set forth in SEQ ID NO: 29.

In some instances, the glass stabilization agent is selected from trehalose, sucrose, raffinose, inulin, dextran, mannitol, and cyclodextrin.

In some instances, the glass stabilization agent is trehalose.

In some instances, the trehalose is at a percent (w/w) concentration to make up to about 100%.

In some instances, the composition does not comprise a surfactant.

In some instances, the pharmaceutical composition comprises:

- 5 a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 20 h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
- 25

In some instances, the pharmaceutical composition comprises:

- a. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 30 b. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- c. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 35 e. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- f. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 40

- h. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- i. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.

5 When the pharmaceutical composition comprises about 3.14% (w/w) histidine, the pharmaceutical composition may comprise about 0.55% (w/w) L-histidine and about 2.59% (w/w) histidine HCl. In some instances, when the pharmaceutical composition comprises 3.14% (w/w) histidine, the pharmaceutical composition may comprise 0.55% (w/w) L-histidine and 2.59% (w/w) histidine HCl.

In some instances, following reconstitution, the number of sub-visible particles between 5 μ m to 200 μ m is less than about 2.5×10^4 /ml.

In some instances, following reconstitution, the number of sub-visible particles between 5 μ m to 200 μ m is less than about 0.5×10^4 /ml.

In some instances, following reconstitution, the number of sub-visible particles between 10 μ m to 200 μ m is less than about 1×10^4 /ml.

15 In some instances, following reconstitution, the number of sub-visible particles between 10 μ m to 200 μ m is less than about 0.2×10^4 /ml.

In some instances, following reconstitution, the number of sub-visible particles between 25 μ m to 200 μ m is less than about 2×10^3 /ml. For example, following reconstitution, the number of sub-visible particles between 25 μ m to 200 μ m is less than about 0.2×10^3 /ml.

20 In some instances, the number of sub-visible particles is determined by dynamic flow imaging microscopy, optionally by microflow imaging (MFI).

In some instances, the number of sub-visible particles is determined following reconstitution in water, to an antigen-binding fragment concentration of either 2.5 mg/ml or 30 mg/ml.

25 In a second aspect, the disclosure provides a process for making a pharmaceutical composition for inhalation, comprising:

- a. Providing an aqueous solution of about pH 5 to about pH 6 comprising leucine, trileucine, histidine, a glass stabilization agent and an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody;
- b. Spray drying the aqueous solution of (a) to produce dry powder particles; and
- c. Collecting the dry powder particles;

30 wherein the aqueous solution comprises about 5% (w/w) to about 15% (w/w) leucine, about 1% (w/w) to about 5% (w/w) trileucine, about 1% (w/w) to about 10% (w/w) histidine, about 5% (w/w) to about 50% (w/w) antigen binding fragment and % (w/w) glass stabilization agent to 100% total solids content.

35 In some instances, the aqueous solution has a pH of 5.5.

In some instances, the glass stabilization agent is trehalose.

In some instances, the aqueous solution comprises:

- a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
or
- 20 i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.

In a third aspect, the present disclosure provides a dry powder formulation obtained by the process of the second aspect of the disclosure.

- 15 In a fourth aspect, the present disclosure provides a method of treating a TSLP-related condition in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect of the present disclosure. The present disclosure also provides a pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect for use in treating a TSLP-related conditions. In addition, the disclosure provides the use of the pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect in the
- 30 manufacture of a medicament for the treatment of a TSLP-related condition.

In some instances, the TSLP-related condition is asthma, COPD, allergic rhinitis, allergic rhinosinusitis, allergic conjunctivitis, eosinophilic esophagitis, chronic spontaneous urticaria or chronic rhinosinusitis.

In some instances, the TSLP-related condition is asthma.

In some instances, the TSLP-related condition is COPD.

- 35 In a fifth aspect, the present disclosure provides a method for improving lung function in a subject with asthma or COPD, the method comprising administering to the subject a pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect of the present disclosure. The present disclosure also provides a pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect for use in a method of improving lung function in a patient with asthma or COPD. In addition,
- 40 the disclosure provides the use of the pharmaceutical composition of the first aspect or the dry powder

formulation of the third aspect in the manufacture of a medicament for improving lung function in a patient with asthma or COPD.

In some instances, improvement of lung function means one or more of the following parameters: improvement compared to baseline of (i) pre-bronchodilator (BD) FVC, (ii) post-BD-FVC, (iii) pre-BD-FEV₁,
5 (iv) post-BD FEV₁, (v) mean morning PEF and/or (vi) mean evening PEF.

In a sixth aspect, the present disclosure relates to a method for improving symptoms of asthma or COPD in a subject in need thereof, the method comprising administering to the subject a pharmaceutical composition of the first aspect or the dry powder formulation of the third aspect of the present disclosure.

In some instances, improving symptoms of asthma means one of the following parameters: improvement
10 compared to baseline (i) mean asthma symptom diary score, (ii) Asthma Control Questionnaire 6 (ACQ-6) score, (iii) Asthma Quality of Life Questionnaire (AQLQ) score, and/or (iv) St. George's Respiratory Questionnaire (SGRQ) score.

In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the asthma is moderate to severe asthma.

15 In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the pharmaceutical composition or the dry powder formulation is administered by inhalation or intranasally. In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the pharmaceutical composition is administered by dry powder inhaler.

In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the pharmaceutical
20 composition or the dry powder formulation to be administered to the subject comprises a dose of about 0.2 mg to about 16 mg of the antigen binding fragment of the anti-TSLP antibody. In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the pharmaceutical composition or the dry powder formulation to be administered to the subject comprises a dose of about 0.4 mg to about 8 mg of the antigen binding fragment of the anti-TSLP antibody. In some instances of any of the fourth, fifth and sixth aspects
25 of the disclosure, the pharmaceutical composition or the dry powder formulation is administered or is to be administered to the subject comprises a dose of about 0.4 mg, about 2 mg or about 8 mg of the antigen binding fragment of the anti-TSLP antibody.

In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the asthma is uncontrolled moderate to severe asthma.

30 In some instances of any of the fourth, fifth and sixth aspects of the disclosure, the pharmaceutical composition or the dry power formulation is administered or is to be administered to the subject once daily (Q1D) by inhalation.

The disclosure includes the combination of the aspects and features described except where such a combination is clearly impermissible or expressly avoided.

35 ***Summary of the Figures***

Instances and experiments illustrating the principles of the disclosure will now be discussed with reference to the accompanying figures in which:

Figure 1 shows Scanning Electron Microscope (SEM) images of formulations tested in study 1.

Figures 2A and 2B show the Micro Flow Imaging (MFI) results for 10% bulk powder reconstituted in water for injection to the (**FIG. 2A**) 2.5 mg/ml protein and to (**FIG. 2B**) feedstock concentration (7.5mg/ml protein). Results are expressed as particle counts per ml as an average of three replicates.

5 **Figures 3A and 3B** show the MFI results for 40% bulk powder (BP) reconstituted in water for injection to the (**Fig. 3A**) 2.5 mg/ml protein and to (**Fig. 3B**) feedstock concentration (30 mg/ml protein). Results are expressed as particle counts per ml as an average of three replicates.

Figures 4A, 4B, and 4C show the MFI results for (**Fig. 4A**) drug substance (DS) and (**Fig. 4B**) 10% and (**Fig. 4C**) 40% FAB1 reconstituted BP at feedstock protein concentration (7.5 mg/ml for 10% formulations
10 and 30 mg/ml for 40% formulation).

Figures 5A, 5B, and 5C show the MFI results for 10% and 40% FAB1 BP at 2.5 mg/ml protein concentration across different formulations: (**Fig. 5A**) TLTC pH 5 at a concentration of 2.5 mg/ml; (**Fig. 5B**) TLTH pH 6 at a concentration of 2.5 mg/ml; (**Fig. 5C**) TLTH pH 5 at a concentration of 2.5 mg/ml.

Figures 6A and 6B show (**Fig. 6A**) Next Generation Pharmaceutical Impactor (NGI) results for 10% FAB1 plotted by stage and (**Fig. 6B**) a summary of the results. The Next Generation Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.
15

Figures 7A and 7B show (**Fig. 7A**) Next Generation Pharmaceutical Impactor (NGI) results for 10% FAB1 plotted by stage and (**Fig. 7B**) a summary of the results. The Next Generation Pharmaceutical Impactor (NGI) is as described in USP <601> Apparatus 6.

20 **Figure 8** shows study 2 40% FAB1 SEM images.

Figure 9 shows study 2 10% FAB1 SEM images.

Figures 10A and 10B show the study 2 subvisible particles (SVP) detected by MFI for 10% FAB1 formulations reconstituted to (**Fig. 10A**) 2.5mg/ml, or (**Fig. 10B**) the feedstock concentration of 7.5 mg/ml. Particle counts are expressed as particles/ml in BP for the listed sizes (no larger than (NLT) 2, 5, 10, 25
25 μm).

Figures 11A and 11B show the study 2 MFI results for 40% FAB1 formulations reconstituted to (**Fig. 11A**) 2.5mg/ml, or (**Fig. 11B**) 30 mg/ml (feedstock concentration). Particle counts are expressed as particles/ml in BP for the listed sizes (no larger than (NLT) 2, 5, 10, 25 μm).

Figures 12A and 12B show (**Fig. 12A**) Next Generation Pharmaceutical Impactor (NGI) results for study 2 10% FAB1 plotted by stage; and (**Fig. 12B**) a summary of the results. The Next Generation Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.
30

Figures 13A and 13B show (**Fig. 13A**) Next Generation Pharmaceutical Impactor (NGI) results for study 2 40% FAB1 plotted by stage, and (**Fig. 13B**) a summary of the results. The Next Generation

Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.

Figure 14 shows study 3 SEM images.

Figures 15A and 15B shows study 3 MFI results 10% FAB1 reconstituted to (**Fig. 15A**) 2.5mg/ml, or (**Fig. 15B**) the feedstock concentration of 7.5 mg/ml. Particle counts are expressed as particles/ml in BP for the listed sizes (no larger than (NLT) 2, 5, 10, 25 µm). Results are shown as the average of triplicate samples.

Figures 16A and 16B show study 3 SVP detected by MFI for 40% FAB1 formulations reconstituted to (**Fig. 16A**) 2.5mg/ml, or (**Fig. 16B**) the feedstock concentration of 30 mg/ml. Particle counts are expressed as particles/ml in BP for the listed sizes (no larger than (NLT) 2, 5, 10, 25 µm). Results are shown as the average of triplicate samples.

Figures 17A and 17B show study 3 NGI results of (**Fig. 17A**) 10% FAB1 plotted by stage (Lot 21-WS-055, 056 and 057), (**Fig. 17B**) 40% FAB1 plotted by stage (Lot 21-WS-061, 058 and 059), and (**Fig. 17C**) a summary of the results. The Next Generation Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.

Figure 18 shows study 4 stability (1 month accelerated conditions) SEM images.

Figures 19A and 19B shows study 4 NGI results of 10% FAB1 (**Fig. 19A**) TLTH 1.3% His; (**Fig. 19B**) TLTH 3.15% His, (**Fig. 19C**) TLTH 5% plotted by stage. The Next Generation Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.

Figures 20A and 20B shows study 4 NGI results of 40% FAB1 (**Fig. 20A**) TLTH 1.3% His; (**Fig. 20B**) TLTH 3.14% His, (**Fig. 20C**) TLTH 5% plotted by stage. The Next Generation Pharmaceutical Impactor (NGI) is as described in United States Pharmacopeia (USP) <601> Apparatus 6.

Figure 21 shows perivascular/peribronchiolar mononuclear inflammatory cell infiltrates (arrows) with macrophage aggregates (triangles) in a mouse receiving 7.1 mg/kg/day FAB1 in TLTC, pH 6 with PS80 compared with a placebo control, labelled as "2M 2001, placebo".

Figure 22 shows visible particles in the reconstituted FAB1 TLTC, pH 6 with PS80 in water.

Figure 23 shows representative images FAB1-related lung pathology for the second toxicity study, at the indicated dose levels (placebo, 4mg/kg, and 9.2 mg/kg). Arrows for the lung images point to mononuclear cell (MNC) infiltrates.

Figure 24 lists the pathology results for the second toxicity study.

Figure 25 FeNO Mean Change from Baseline by Dose Over Time, GLS Means (80% confidence interval (CI)) – Results from Part B of Study described in Example 7

Figure 26A Pre-BD FEV1 (L) - mean change from baseline over time measured in the clinic, LS means - Results from Part B of Study described in Example 7

Figure 26B Pre-BD FEV1 (L) - mean change from baseline over time measured in the clinic, LS means - Results from the high dose arm (top – 8mg) or placebo (bottom) Part B of Study described in Example 7

Figure 27 ACQ-6 Change from Baseline by Dose Over Time, least squares (LS) means (80% confidence interval (CI)) – Results from the high dose arm (top – 8mg) or placebo (bottom) Part B of Study described in Example 7

Figure 28 FAB1 popPK model schematic. k_a = absorption rate constant, F1 and F2 = first order and zero order absorption bioavailability respectively, D2 = duration of zero order absorption, CL = Clearance, Q1 and Q2 = intercompartmental clearances, Vc, V1 and V2 = Volume of the central compartment, peripheral compartment 1 and peripheral compartment 2 respectively. Observations are the dotted line.

Figure 29 FAB1 predicted serum (dashed line) and lung concentration (solid line) following inhaled 0.4, 2 and 8mg QD administration. Grey shaded area is a visualisation aid to separate serum and lung predictions. Horizontal dotted line is the predicted lung Cave concentration of tezepelumab following SC 210mg administration (Q4W).

Figure 30 shows a Phase 2b protocol design for testing the efficacy of an anti-TSLP Fab fragment.

Detailed Description

Aspects and instances of the present disclosure will now be discussed with reference to the accompanying figures. Further aspects and instances will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Pharmaceutical Compositions

As described herein, pharmaceutical compositions are provided for the stabilization and delivery of pharmaceutical active agents. Suitably, the pharmaceutical compositions are formulated for pulmonary delivery, including via inhalation via a dry powder inhaler (DPI). Accordingly, the pharmaceutical composition comprises a “dry powder formulation”.

The pharmaceutical compositions provided herein comprise spray-dried particles, the particles comprising: about 5% (w/w) to about 15% (w/w) leucine; about 1% (w/w) to about 5% (w/w) trileucine; about 1% (w/w) to about 10% (w/w) histidine buffer at a pH of between about pH 5 to pH 6; about 1% (w/w) to about 80% (w/w) of an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody; and a glass stabilisation agent.

“Pharmaceutical composition” as used herein refers to a preparation which is in such form as to permit the biological activity of the active ingredient (e.g., an anti-TSLP Fab disclosed herein) to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the composition would be administered. Such composition can be sterile.

As used herein "spray dried particles" refers to particles manufactured in a process that uses an aerosol phase to spray dry particles to form the basis for dry dosage forms. The spray-dried particles thus refer to a plurality of solid microparticles in a powder composition that suitably contains less than about 20% moisture, more suitably less than 10% moisture, less than about 5-6% moisture, or less than about 3% moisture. As described herein, the pharmaceutical compositions can be utilized for delivery via inhalation to a patient. In other instances, the pharmaceutical compositions can be reconstituted and administered in a liquid form, either orally, intravenously, parenterally, etc. An exemplary process of preparing spray-dried particles, in accordance with instances hereof may take place as follows. A liquid feedstock containing the desired final components of the dry powder formulation are atomized using an atomizer, to a fine mist. The mist is then dried as described herein. The atomized droplets contain the dissolved components, initially as a liquid droplet. As the droplet dries, different components of the formulation begin to saturate and precipitate at varying rates. As described herein, a shell begins to form around an outer surface of the microparticles of the dry powder formulations. This shell suitably includes the leucine and trileucine components at an outer surface of the shell. It should be noted that leucine and trileucine become preferentially located at an outer surface of the microparticles, while smaller amounts of leucine and trileucine can also be found throughout the microparticles. In instances, a higher concentration of leucine and trileucine are suitably found at or near the surface of the microparticles, rather than near the center of the microparticles. In instances, the center of particles contains a substantial amount of the active agent, along with other excipient components as described herein, suitably in an amorphous form. As used herein, a "substantial amount" of the active agent means at least about 60% of the active agent (i.e., of the total active agent in the formulation) is located at or near the center of the microparticles, suitably at least about 70%, and more suitably at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, and in instances about 95%-100%, of the active agent is located at or near the center of the microparticles.

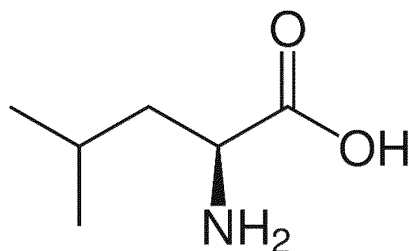
A "microparticle" as used herein refers to a solid particle having a size mass mean diameter (MMD) of less than 20 μm . Mass mean diameter is a measure of the mean particle size of the microparticles, measured using a suitable method, including for example centrifugal sedimentation, electron microscopy, light scattering, laser diffraction, etc.

Unless otherwise stated, "active agent" refers to an antigen binding fragment derived of an anti-TSLP antibody, as defined herein.

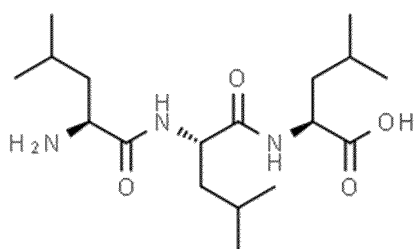
Unless otherwise stated, the ratios described herein are expressed as ratios by weight % (w/w – also referred to as a "weight ratio"). The amounts of leucine, trileucine, histidine buffer, and antigen -binding fragment of an anti-TSLP antibody provided herein, unless otherwise stated, are provided as weight percentages (wt %) of the formulations. As the pharmaceutical compositions described herein contain substantially little if any water, the weight components of the pharmaceutical compositions are thus dry weight percentages of the final formulations.

The ratios are achieved by providing a desired mg/mL concentration of these components in a feedstock, and then spray drying to remove the feedstock solvent resulting in an atomized microparticle where the starting concentration ratio (expressed in mg/mL), is maintained as a final ratio by weight.

- As used herein "leucine," whether present as a single amino acid or as an amino acid component of a peptide, refers to the amino acid leucine (C₆H₁₃NO₂), which may be a racemic mixture or in either its D- or L-form, as well as modified forms of leucine (i.e., where one or more atoms of leucine have been substituted with another atom or functional group). The chemical structure of leucine is provided below:



- "Trileucine" as utilised herein refers to the chemical compound in which three leucine molecules are linked together in a peptide, as leucine-leucine-leucine (Leu-Leu-Leu), C₁₈H₃₅N₃O₄. The chemical structure of trileucine is provided below:



- Exemplary weight percentages for leucine and trileucine that can be utilised in the pharmaceutical compositions to achieve the desired ratios are described herein. Suitably, the dry powder formulations comprise about 5% to about 15% leucine and about 1% to about 5% trileucine. The pharmaceutical compositions described herein comprise about 5% to about 15% leucine by weight, more suitably about 5% to about 14%, about 5% to about 13%, about 5% to about 12%, about 5% to about 11%, about 5% to about 10%, about 5% to about 9%, about 5% to about 8%, about 5% to about 7%, about 5% to about 6%, about 6% to about 15%, about 7% to about 15%, about 8% to about 15%, about 9% to about 15%, about 10% to about 15%, about 11% to about 15%, about 12% to about 15%, about 13% to about 15%, about 14% to about 15%, about 5% to about 14%, about 6% to about 14%, about 7% to about 14%, about 8% to about 14%, about 9% to about 14%, about 10% to about 14%, about 11% to about 14%, about 12% to about 14%, about 13% to about 14%, about 5% to about 13%, about 6% to about 13%, about 7% to

about 13%, about 8% to about 13%, about 9% to about 13%, about 10% to about 13%, about 11% to about 13%, about 11% to about 13%, about 12% to about 13%, about 5% to about 12%, about 6% to about 12%, about 7% to about 12%, about 8% to about 12%, about 9% to about 12%, about 10% to about 12%, about 11% to about 12%, about 5% to about 11%, about 6% to about 11%, about 7% to about 11%, about 8% to about 11%, about 9% to about 11%, about 10% to about 11%, about 5% to about 10%, about 6% to about 10%, about 7% to about 10%, about 8% to about 10%, about 9% to about 10%, about 5% to about 9%, about 6% to about 9%, about 7% to about 9%, about 8% to about 9%, about 5% to about 8%, about 6% to about 8%, about 7% to about 8%, about 5% to about 7%, about 6% to about 7%, about 5% to about 6%, about 5%, about 5.5%, about 6%, about 6.5%, about 7%, about 7.5%, about 8%, about 8.5%, about 9%, about 9.5%, about 10%, about 10.5%, about 11%, about 11.5%, about 12%, about 12.5%, about 13%, about 13.5%, about 14%, about 14.5%, about 15% leucine by weight. In some instances, the pharmaceutical compositions described herein comprise about 10.5% leucine by weight. In some instances, the pharmaceutical compositions described herein comprise 10.5% leucine $\pm$ 1%, 10.5% leucine $\pm$ 2%, 10.5% leucine $\pm$ 3%, 10.5% leucine $\pm$ 4%, 10.5% leucine $\pm$ 5%, 10.5% leucine $\pm$ 10%, by weight.

The pharmaceutical compositions comprise about 1% to about 5 % trileucine by weight, more suitably about 1% to about 4%, about 1% to about 3%, about 1% to about 2%, about 2% to about 4%, about 2% to about 3%, about 3% to about 5%, about 3% to about 4%, about 4% to about 5%, about 1%, about 3%, about 4%, about 5% trileucine, by weight. In some instances, the pharmaceutical compositions described herein comprise about 2% leucine by weight. In some instances, the pharmaceutical compositions described herein comprise 2% leucine $\pm$ 0.5%, 2% leucine $\pm$ 1%, 2% leucine $\pm$ 2%, 2% leucine $\pm$ 3%, 2% leucine $\pm$ 4%, 2% leucine $\pm$ 5%, 2% leucine $\pm$ 10%, by weight.

In some instances, the pharmaceutical compositions comprise about 8% to about 12% leucine and about 1% to about 3% trileucine, and in some instances, the pharmaceutical compositions comprise about 10.5% leucine and about 2% trileucine.

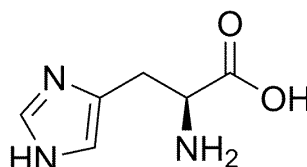
In further instances, the particles contain leucine and trileucine located substantially throughout the microparticles, but with higher amounts at or near the surface of the microparticles. As used herein "substantially throughout the microparticles" means that the leucine and/or trileucine are located in a gradient from the outer surface of the microparticles toward the center of the microparticles, but suitably with decreasing amounts of the leucine and/or trileucine as you move toward the center, and in instances, no leucine or trileucine are found at the center of the microparticles where the active agent is located. In other instances, the amounts and leucine and trileucine can be substantially uniform throughout a cross-section of the microparticles.

In instances, substantially each of the particles of the pharmaceutical composition comprises leucine and trileucine. That is, suitably at least about 60% of the microparticles contain leucine and trileucine, or at least about 70%, and more suitably at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, and in instances about 95%-100%, of the microparticles comprise leucine

and trileucine. In instances each of the microparticles of the dry powder formulations comprise leucine and trileucine.

In additional cases, leucine and/or trileucine can be found in pharmaceutical compositions, but not contained within or associated with a microparticle of the formulation. Thus, in instances, free leucine and/or trileucine that is not associated with a microparticle can be found in the dry powder formulations. However, in general, the amount of free leucine and/or trileucine (i.e., not associated with a microparticle) is on the order of less than about 10%, less than about 5%, less than about 1%, and more suitably less than about 0.1% of the total amount of leucine and/or trileucine in the formulations.

“Histidine” whether present as a single amino acid or as an amino acid component of a peptide, refers to the amino acid histidine (C₆H₉N₃O₂), which may be a racemic mixture or in either its D- or L-form, as well as modified forms of histidine (i.e., where one or more atoms of leucine have been substituted with another atom or functional group). The chemical structure of histidine is provided below.



As described herein, it has been surprisingly found that a pharmaceutical composition comprising a histidine buffer significantly reduced protein aggregation and device and throat deposition, at least partly by reducing the level of subvisible particles, compared with a reference buffer. Accordingly, the pharmaceutical compositions described herein comprise a histidine buffer. Suitably the histidine buffer is present at about 1% to about 10%, for example the histidine buffer may be present at about 1% to about 9%, about 1% to about 8%, about 1% to about 7%, about 1% to about 6%, about 1% to about 5%, about 1% to about 4%, about 1% to about 3%, about 1% to about 2%, about 2% to about 10%, about 2% to about 9%, about 2% to about 8%, about 2% to about 7%, about 2% to about 6%, about 2% to about 5%, about 2% to about 4%, about 2% to about 3%, about 2% to about 3.5%, or about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 5.5%, or about 6, about 6.5%, about 7%, about 7.5%, about 8%, about 8.5%, about 9%, about 9.5% by weight. In certain instances, the pharmaceutical composition comprises about 3.14% histidine buffer by weight. In some instances, the pharmaceutical compositions described herein comprise 3.14% histidine buffer $\pm$ 0.5%, 3.14% histidine buffer $\pm$ 1%, 3.14% histidine buffer $\pm$ 2%, 3.14% histidine buffer $\pm$ 3%, 3.14% histidine buffer $\pm$ 4%, 3.14% histidine buffer $\pm$ 5%, 3.14% histidine buffer $\pm$ 10%, by weight. In some instances, the pharmaceutical composition comprises about 3.14% histidine buffer $\pm$ 10%, by weight (w/w). In some instances, the pharmaceutical composition comprises about 3.14% histidine buffer, by weight (w/w). In some instances, the pharmaceutical composition comprises about 0.55% (w/w) L-histidine and 2.59% (w/w) histidine HCl.

A "reference buffer" as used herein is a buffer that does not contain histidine at the ratios described herein, for example, a reference buffer may not comprise any histidine buffer. In some instances, the reference buffer comprises citrate. In some instances, the reference buffer comprises trehalose, leucine, trileucine and citrate (TLTC). In some instances, the reference buffer has a pH of about pH 6. In some instances, the reference buffer comprises a surfactant, for example polysorbate 80 (PS80).

The histidine buffers also provide control of the pH of the pharmaceutical composition, suitably maintaining a pH of about pH 5.5 to about pH 6, such as about pH 5.5, about pH 5.6, about pH 5.7, about pH 5.8, about pH 5.9. In certain instances, the pH of the histidine buffer is 5.5.

The compositions described herein comprise an antigen binding fragment of an anti-thymic stromal lymphopoietin (anti-TSLP) antibody. Advantageously, the inventors have found that the formulations described herein enable delivery of the antigen binding fragment via inhalation directly into the lung. Delivery of a therapeutically active antigen binding fragment of an anti-TSLP antibody via inhalation allows for the use of biologic medicines for the treatment of asthma in a primary care setting. Suitably, the antigen binding fragment is present at about 1% to about 80%, for example the antigen binding fragment may be present at about 1% to about 50%, at about 1% to about 45% about 1% to about 40%, about 2% to about 50%, 2% to about 45% or about 2% to about 40% by weight (w/w).

In some instances, the antigen binding fragment is present in the pharmaceutical composition at a concentration of about 1% to about 10% by weight (w/w), about 1% to about 9% by weight (w/w), about 1% to about 8% by weight (w/w), about 1% to about 7% by weight (w/w), about 1% to about 6% by weight (w/w), about 1% to about 5% by weight (w/w), of about 1% to about 4% by weight (w/w), about 1% to about 3% by weight (w/w), about 2% to about 10% by weight (w/w), about 2% to about 9% by weight (w/w), about 2% to about 8% by weight (w/w), about 2% to about 7% by weight (w/w), about 2% to about 6% by weight (w/w), about 2% to about 5% by weight (w/w), about 2% to about 4% by weight (w/w), about 2% to about 3% by weight (w/w), about 3% to about 10% by weight (w/w), about 3% to about 9% by weight (w/w), about 3% to about 8% by weight (w/w), about 3% to about 7% by weight (w/w), about 3% to about 6% by weight (w/w), about 3% to about 5% by weight (w/w), about 3% to about 4% by weight (w/w), about 4% to about 10% by weight (w/w), about 4% to about 9% by weight (w/w), about 4% to about 8% by weight (w/w), about 4% to about 7% by weight (w/w), about 4% to about 6% by weight (w/w), about 4% to about 5% by weight (w/w), about 5% to about 10% by weight (w/w), about 5% to about 9% by weight (w/w), about 5% to about 8% by weight (w/w), about 5% to about 7% by weight (w/w), about 5% to about 6% by weight (w/w), about 5% to about 15% by weight (w/w), about 6% to about 14% by weight (w/w), about 7% to about 13% by weight (w/w), about 8% to about 12% by weight (w/w), about 9% to about 11% by weight (w/w), about 10% to about 20% by weight (w/w), about 10% to about 30% by weight (w/w), about 10% to about 40% by weight (w/w), about 15% to about 25% by weight (w/w), about 25% to about 35% by weight (w/w), or about 35% to about 45% by weight (w/w)).

In some instances, the antigen binding fragment is present in the pharmaceutical composition at a concentration of about 1%, about 2% about 3% about 4%, about 5%, about 6%, about 7%, about 8%,

- about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% or about 80% by weight (w/w). In certain instances, the antigen binding fragment is present in the pharmaceutical composition at a concentration of about 1% (w/w) to about 80% (w/w), for example about 1% (w/w) to about 40% (w/w). In
- 5 some instances, the antigen binding fragment is present in the pharmaceutical composition at a concentration of about 1% (w/w), about 2% (w/w), about 3% (w/w), about 10% (w/w), about 15% (w/w), about 20% (w/w), about 25% (w/w), about 30% (w/w), about 35% (w/w), about 40% (w/w), about 45% (w/w), about 50% (w/w), about 55% (w/w), about 60% (w/w), about 65% (w/w), about 70% (w/w), about 75% (w/w) or about 80% (w/w).
- 10 The pharmaceutical compositions described herein further comprise a glass stabilization agent to aid in stabilizing the formulation, and in particular, in stabilising the active agent. A "glass stabilisation agent" refers to an excipient that stabilizes an active agent (suitably a polypeptide) in a dry powder formulation, suitably by substituting for water at the active agent surface during drying, or otherwise impeding the degradation process, and forms an amorphous solid that includes the active agent. Examples of glass
- 15 stabilization agents include amorphous saccharides, polymeric sugars, buffers, salts, or synthetic polymers (e.g., poly-L-glycolic acid), as well as mixtures of such components. In instances, the glass stabilization agent is an amorphous saccharide. In additional instances, the glass stabilization agent is a buffer. In still further instances, the formulations described herein can include both an amorphous saccharide and a buffer, which together or separately may act as a glass stabilization agent.
- 20 Exemplary amorphous saccharides for use in the compositions described herein include, but are not limited to, trehalose, sucrose, raffinose, inulin, dextran, mannitol, and cyclodextrin. Suitably the amorphous saccharide is present at about 30% to about 70% (weight percentage) of the dry powder formulation. In further instances, the amorphous saccharide is present at about 30% to about 65%, about 35% to about 65%, about 35% to about 60%, about 40% to about 60%, about 30% to about 50%, or
- 25 about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, or about 60%. Suitably the amorphous saccharide is trehalose, and is present in the formulations at about 30%-60%, more suitably about 35%-55%, or about 35%, about 40%, about 45% or about 50%, of the weight of the dry powder formulation.
- In compositions and formulations that "consist essentially" of the recited ingredients, such compositions
- 30 and formulations contain the recited components and those that do not materially affect the basic and novel characteristics of the claimed formulations. Components that do not materially affect the basic and novel characteristics of the claimed compositions are those that do not limit the ability of the leucine and trileucine to stabilize the dry powder formulations. Suitably, compositions and formulations that consist essentially of the recited ingredients specifically exclude other amino acids or tripeptide amino acids, but
- 35 can include additional sugars, buffers, etc.

In exemplary instances, a pharmaceutical composition is provided that comprises:

- a. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 85.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- b. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 c. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 81.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 f. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 h. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 81.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- i. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 79.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- j. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 20 k. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- l. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 25 m. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 54.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- n. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 52.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 30 o. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 56.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- p. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 35 q. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- r. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 40 s. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 4.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- t. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 2.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or

- u. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 6.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.

In some instances, a pharmaceutical composition is provided that comprises:

- 5 a. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 85.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- b. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- c. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- 10 d. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 84.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- e. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 82.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- f. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 80.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- 15 g. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- h. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 20 i. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 79.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- j. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 76.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- k. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 74.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 25 l. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 72.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- m. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 54.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 30 n. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 52.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- o. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 56.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- p. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 44.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 35 q. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 42.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- r. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 46.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- 40 s. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 4.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- t. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 2.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5; or

- u. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 6.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5.

In some instances, a pharmaceutical composition is provided that comprises 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5.

In some instances, a pharmaceutical composition is provided that comprises 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 74.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5.

In some instances, a pharmaceutical composition is provided that comprises 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 42.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5.

In some instances, the pharmaceutical composition is provided that comprises:

- a. 0.2 mg (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 85.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- b. 0.2 mg (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- c. 0.2 mg (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 81.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- f. 0.4 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- h. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- i. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 79.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- j. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;

- k. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- l. 2 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 m. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 54.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- n. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 52.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- 10 o. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 56.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- p. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- q. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 r. 8 mg antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5
- s. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 4.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- t. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 2.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5; or
- 20 u. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 6.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5.

In these instances, the total mass solids content of the pharmaceutical composition is 20 mg.

In some instances, the pharmaceutical composition comprises:

- 25 a. 0.2 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 85.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- b. 0.2 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- c. 0.2 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- 30 d. 0.4 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 84.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- e. 0.4 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 82.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 35 f. 0.4 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 80.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- g. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- h. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 40 i. 0.6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 79.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;

- j. 2 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 76.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
 - k. 2 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 74.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
 - 5 l. 2 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 72.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
 - m. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 54.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
 - 10 n. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 52.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
 - o. 6 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 56.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
 - p. 8 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 44.4% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
 - 15 q. 8 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 42.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
 - r. 8 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 46.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5; or
 - 20 s. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 4.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
 - t. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 2.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5; or
 - u. 16 mg (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 6.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5.
- 25 In these instances, the total mass solids content of the pharmaceutical composition is 20 mg.

In some instances, a pharmaceutical composition is provided that comprises 0.4 mg $\pm$ 20% antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 0.4 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5. In these instances, the total mass solids content of the pharmaceutical composition is 20 mg.

In some instances, a pharmaceutical composition is provided that comprises 2 mg $\pm$ 20% antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 2 mg antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 74.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5. In these instances, the total mass solids content of the pharmaceutical composition is 20 mg.

In some instances, a pharmaceutical composition is provided that comprises 8 mg $\pm$ 20% antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5. In some instances, the pharmaceutical composition comprises 8 mg antigen binding fragment, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5. In these instances, the total mass

solids content of the pharmaceutical composition is 20 mg. When the pharmaceutical composition disclosed herein comprises about 3.14% (w/w) histidine, the pharmaceutical composition may comprise about 0.55% (w/w) L-histidine and about 2.59% (w/w) histidine HCl. In some instances, when the pharmaceutical composition comprises 3.14% (w/w)) histidine, the pharmaceutical composition may
5 comprise 0.55% (w/w) L-histidine and 2.59% (w/w) histidine HCl.

The particles that make up the pharmaceutical compositions described herein suitably have a specified mass median aerodynamic diameter (MMAD) when provided in aerosol form. The microparticles may also have a specified equivalent optical volume mean diameter (oVMD). oVMD may also be referred to as particle size distribution (PSD or pPSD).

10 As used herein, "mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed microparticle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior and is the diameter of a unit density sphere having the same settling velocity, in air, as the microparticle. The aerodynamic diameter encompasses particle shape, density and physical size of a microparticle. As used herein, MMAD refers to the midpoint or median of the
15 aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction, unless otherwise indicated. Suitably the microparticles of the dry powder formulations provided herein have a mass median aerodynamic diameter (MMAD) of about 1 μm to about 10 μm , more suitably about 2 μm to about 8 μm , about 2 μm to about 7 μm , about 2 μm to about 6 μm , about 2 μm to about 5 μm , about 2 μm to about 4 μm , about 3 μm to about 7 μm , about 4 μm to about 7 μm , about 3 μm to about 6 μm , or about
20 2 μm , about 3 μm , about 4 μm , about 5 μm , about 6 μm , or about 7 μm .

Suitably, the fine particle fraction (the fraction of particles emitted from an inhalation device having an aerodynamic particle diameter of less than 5 μm of the dry powder formulations described herein is $\geq$ 50%, more suitably $\geq$ 60%. This fine particle fraction (FPF) may contribute to a low device retention of the dry powder formulations of less than 20%, suitably less than 15%, less than 10%, or less than 5%,
25 remaining in a device following delivery to a patient.

In additional instances, the spray-dried particles suitably have an equivalent optical volume mean diameter (oVMD) of about 0.5 μm to about 7 μm . Equivalent optical volume mean diameter (oVMD) refers the mean diameter of a sphere that best approximates a specific optical interaction of the particle with light, where half of the microparticles are best approximated by an equivalent sphere smaller, and half of
30 the microparticles are best approximated by an equivalent sphere larger than the mean, when measured using a suitable optical technique. In exemplary instances, the microparticles have an equivalent optical volume mean diameter (oVMD) of about 0.5 μm to about 6 μm , or about 1 μm to about 5 μm , or about 1 μm to about 4 μm , or about 2 μm to about 4.5 μm , or about 2.5 μm to about 4 μm , or about 2 μm to about 4 μm , or about 2 μm to about 3 μm , or about 2 μm to about 3.5 μm , or about 1 μm , about 1.5 μm , about 2
35 μm , about 2.5 μm , about 3 μm , about 3.5 μm , about 4 μm , about 4.5 μm , or about 5 μm .

The use of leucine and trileucine in the dry powder formulations also results in microparticles having the desired sizes (MMAD), as well as desirable specific surface area (SSA) and roughness, resulting in microparticles that can flow appropriately and be delivered to the lungs using various inhalation platforms.

Specific surface area (SSA) of the microparticles is defined as the total surface area of the microparticles per unit of mass (suitably with units of m^2/g). Methods of measuring SSA are known in the art, and include for example Brunauer–Emmett–Teller (BET) measurements using specific surface area evaluation of materials by nitrogen adsorption measured as a function of relative pressure. The surface area is determined by calculating the amount of adsorbate gas corresponding to a monomolecular layer on the surface of the microparticles. The technique measures external area and any pore area evaluations to determine the total specific surface area. Instruments for measuring BET are known in the art.

In some instances, the specific surface area (SSA) of the microparticles of the dry powder formulations is about $3 \text{ m}^2/\text{g}$ to about $8 \text{ m}^2/\text{g}$. In certain instances, the SSA of the plurality of microparticles is about $3.5 \text{ m}^2/\text{g}$ - $7.5 \text{ m}^2/\text{g}$, or about $4 \text{ m}^2/\text{g}$ - $7 \text{ m}^2/\text{g}$, or about $4.5 \text{ m}^2/\text{g}$ - $7 \text{ m}^2/\text{g}$, or about $5 \text{ m}^2/\text{g}$ - $7 \text{ m}^2/\text{g}$, or about $4.5 \text{ m}^2/\text{g}$ - $6 \text{ m}^2/\text{g}$, or about $5 \text{ m}^2/\text{g}$ - $6 \text{ m}^2/\text{g}$, or about $4 \text{ m}^2/\text{g}$, about $4.5 \text{ m}^2/\text{g}$, about $5 \text{ m}^2/\text{g}$, about $5.5 \text{ m}^2/\text{g}$, about $6 \text{ m}^2/\text{g}$, about $6.5 \text{ m}^2/\text{g}$, or about $7 \text{ m}^2/\text{g}$.

In certain instances, the dry powder formulation has a compressed bulk density of about 0.4 - $1.0 \text{ g}/\text{cm}^3$. Suitably, the compressed bulk density of the dry powder formulation is about 0.5 - $0.8 \text{ g}/\text{cm}^3$. In instances, the compressed bulk density of a dry powder formulation described herein is about 0.4 - $0.9 \text{ g}/\text{cm}^3$, about 0.4 - $0.8 \text{ g}/\text{cm}^3$, about 0.5 - $0.8 \text{ g}/\text{cm}^3$, about 0.6 - $0.8 \text{ g}/\text{cm}^3$, or about $0.4 \text{ g}/\text{cm}^3$, about $0.5 \text{ g}/\text{cm}^3$, about $0.6 \text{ g}/\text{cm}^3$, about $0.7 \text{ g}/\text{cm}^3$, or about $0.8 \text{ g}/\text{cm}^3$. In certain instances, the compressed bulk density of a dry powder formulation described herein is from about $0.4 \text{ g}/\text{cm}^3$ to about $0.9 \text{ g}/\text{cm}^3$. In certain instances, the compressed bulk density of a dry powder formulation described herein is from about $0.5 \text{ g}/\text{cm}^3$ to about $0.8 \text{ g}/\text{cm}^3$.

In certain instances, the pharmaceutical compositions described herein do not comprise a surfactant, such as a polysorbate, e.g. polysorbate-80 or polysorbate-20. While addition of a surfactant minimises the formation of protein aggregates, it increases device deposition, thus reducing lung deposition, and reduces dry-spraying yield. The present inventors optimised the composition described in such a way that omitting the surfactant had minimal effect on protein aggregation while, advantageously, minimising device deposition of the powder (**Example 3**).

It would be apparent to a person skilled in the art that a surfactant reduces the formation of sub-visible particles (SVPs) upon reconstitution of the formulation. In view of this, the minimal device deposition and protein aggregation observed for the composition described herein, which does not comprise a surfactant, is surprising.

A “sub-visible particle” (“SVP”) as referred to herein is a particle not visible to the naked eye of from about $1 \mu\text{m}$ to about $200 \mu\text{m}$. Removing or reducing the formation of SVPs simplifies the analytical characterization of the formulation, as it removes the burden of tracking the formation of SVPs during

manufacturing. The analytical characterization of SVPs may involve the development of orthogonal techniques to identify and quantify SVPs for quality control purposes. Thus, removing SVPs or reducing them to acceptable levels removes the necessity of this characterization step from the manufacturing process, streamlining manufacturing. The removal of SVPs may also make dose ranging more
5 predictable, since the kinetics of drug-release from SVPs is unknown. Furthermore, removing SVPs is likely to increase the amount of active agent available to engage in pharmacological activity post-reconstitution, which may mean not only that a higher delivered dose can be achieved, but a more accurate prediction of the delivered dose can be calculated. A higher delivered dose may also benefit the patient, for example, by potentially reducing the number or frequency of doses that must be delivered for
10 extracting a pharmacological benefit.

The presence of sub-visible particles can be determined by reconstituting a dry powder formulation and the liquid having a cloudy quality. The actual determination of the presence of SVPs can be confirmed using a technique like dynamic flow imaging microscopy, such as microflow imaging (MFI). In MFI (which is also known as flow imaging microscopy (FIM) or dynamic imaging analysis (DIA)), bright-field images
15 are captured in successive frames as a continuous sample stream passes through a flow-cell positioned in the field of view of a microscopic system. The digital images of the particles present in the sample are processed by image morphology analysis software that allows their quantification in size and count. MFI is an established technique for subvisible particle analysis. Dynamic flow imaging microscopy combines microfluidic flow microscopy and high resolution imaging particle analysis to quantify SVP counts. MFI
20 can bin these counts across a particle size range, for example, by binning particles counts in a size range of about 1 to about 200 μm , about 2 μm to about 200 μm , about 5 μm to about 200 μm , about 10 μm to about 200 μm and about 25 μm to about 200 μm . An alternative technique for the measurement of SVP is background membrane imaging (BMI). Briefly, SVPs from a liquid sample are isolated onto a filter surface for counting analysis by a microscope. The BMI software images the baseline prior to particle isolation
25 and, and then subtracts that baseline pixel-by-pixel from the isolated particles so that only photographic information remains (Vargas et al., 2020). Optimisation of the formulation excipients and other aspects of the composition significantly lowered the formation of SVPs.

In certain instances, following reconstitution, the number of SVPs of between 5 μm to 200 μm in size is less than about 30,000 particles per ml, such as 25,000 particles per ml, 20,000 particles per ml, 15,000
30 particles per ml, 10,000 particles per ml or 5,000 particles per ml. In certain instances, the number of SVPs of 5 μm to 200 μm in size are less than 1,000 particles per ml. In certain instances, the number of SVPs of between 5 μm to 200 μm in size are less than below 1,000 particles per ml. In certain instances, the number of SVPs of between 5 μm to about 200 μm in size are less than below 100 particles per ml.

In certain instances, following reconstitution, the number of SVPs of 10 μm to 200 μm in size are less
35 than about 100,000 particles per ml, such as 90,000 particles per ml, 80,000 particles per ml, 70,000 particles per ml, 60,000 particles per ml, 50,000 particles per ml, 40,000 particles per ml or 30,000 particles per ml. In certain instances, the number of SVPs of 10 μm to 200 μm in size are less than about 10,000 particles per ml. In certain instances, the number of SVPs of 10 μm to 200 μm in size are less

than about 2,000 particles per ml. In certain instances, the number of SVPs of 10 μm to about 200 μm in size are less than 100 particles per ml.

In certain instances, following reconstitution, the number of SVPs of 25 μm to 200 μm in size is less than about 200,000 particles per ml, such as 180,000 particles per ml, 170,000 particles per ml, 160,000 particles per ml, 150,000 particles per ml or 140,000 particles per ml. In certain instances, the number of SVPs of about 5 μm to about 200 μm in size are less than about 50,000 particles per ml. In certain instances, the number of SVPs of 5 μm to 200 μm in size are less than about 10,000 particles per ml. In certain instances, the number of SVPs of about 5 μm to about 200 μm in size are less than about 2,000 particles per ml. In certain instances, the number of SVPs of 10 μm to about 200 μm in size are less than about 200 particles per ml.

In some instances, the number of SVPs is determined following reconstitution in water, to an antigen-binding fragment concentration of either 2.5 mg/ml or 30 mg/ml.

In further instances, provided herein is a process for making a pharmaceutical composition for inhalation, comprising: providing an aqueous solution of about pH 5 to about pH 6 comprising leucine, trileucine, histidine, a glass stabilization agent as described herein and an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody; spray drying the aqueous solution of (a) to produce dry powder particles; and collecting the dry powder particles wherein the aqueous solution comprises about 5% (w/w) to about 15% (w/w) leucine, about 1% (w/w) to about 5% (w/w) trileucine, about 1% (w/w) to about 10% (w/w) histidine, about 5% (w/w) to about 50% (w/w) antigen binding fragment and % (w/w) glass stabilization agent to 100% total solids content. In some instances, the aqueous solution has a pH of 5.5.

In certain instances, the aqueous solution comprises:

- a. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 85.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- b. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- c. 1% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 81.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- d. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- f. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 83.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- h. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 81.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;

- 5 i. 3% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 79.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- j. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 k. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- l. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 m. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 54.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- n. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 52.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 o. 30% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 56.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- p. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 20 q. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- r. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 25 s. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 4.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- t. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 2.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- u. 80% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 6.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
- 30 In certain instances, the aqueous solution comprises:
- a. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 85.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- b. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 35 c. 1% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- d. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 84.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- e. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 82.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 40 f. 2% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 80.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;

- g. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 83.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- h. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 81.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- 5 i. 3% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 79.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- j. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 76.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- 10 k. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 74.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- l. 10% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 72.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- 15 m. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 54.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- n. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 52.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- o. 30% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 56.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- 20 p. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 44.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- q. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 42.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5;
- r. 40% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 46.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5;
- 25 s. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 4.36% (w/w) trehalose, and 3.14% (w/w) histidine, at pH 5.5;
- t. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 2.5% (w/w) trehalose, and 5.0% (w/w) histidine, at pH 5.5; or
- 30 u. 80% (w/w) antigen binding fragment, 2% (w/w) trileucine, 10.5% (w/w) leucine, 6.2% (w/w) trehalose, and 1.3% (w/w) histidine, at pH 5.5.

When the aqueous solution comprises about 3.14% (w/w) histidine, the pharmaceutical composition may comprise about 0.55% (w/w) L-histidine and about 2.59% (w/w) histidine HCl. In some instances, when the pharmaceutical composition comprises 3.14% (w/w) histidine, the pharmaceutical composition may comprise 0.55% (w/w) L-histidine and 2.59% (w/w) histidine HCl.

- 35 The aqueous solution is prepared by combining these components in a liquid solvent, to create a feedstock in which each of the components is dissolved. Temperature control may be added as desired or required to increase the solubility of the various components to form the aqueous solution. Exemplary liquid solvents include water, including deionized water, as well as dilute solutions of alcohols with water. In instances, the active agent is suitably added to the aqueous solution after the addition and dissolution
- 40 of the remaining components of the feedstock. The aqueous solution may then be atomized. The aqueous solution may be filtered prior to atomizing. In certain instances, the liquid feedstock may be filtered through a 0.22 micron filter. In certain instances, the aqueous solution comprising leucine,

trileucine, and histidine is filtered prior to the addition of the active agent. In certain instances, the aqueous solution is filtered after the addition of the active agent prior to atomizing. Atomizing refers to converting the solution to fine droplets, suitably using a pressurized gas (such as an inert gas or compressed dry air). Exemplary devices for producing an atomized solution are known in the art and include the use of various atomizing nozzles have desired sizes and flow characteristics. Exemplary parameters for the atomizing including an outlet temperature of about 50°C-90°C, suitably about 60°C-80°C, or about 70°C; a feedstock feed rate of about 8-15 ml/min, suitably about 9-14 ml/min, about 10-13 ml/min, or about 12 ml/min; an atomizer gas flow rate of about 9-15 kg/hour (hr. or h), suitably about 10-14 kg/hr, about 12-14 kg/hr, or about 13 kg/hr; and drying gas flow rate of about 60-100 kg/hr, suitably about 60-90 kg/hr, about 70-90 kg/hr, or about 80 kg/hr.

The atomized solution may then be dried, suitably under heat and in combination with flowing air to aid in the drying. The result of the drying yields a plurality of microparticles. Drying temperatures typically range from about 50°-100°C, or about 60°-100°C, or about 70°-90°C; air flow rate can be on the order of about 10-40 m³/hour.

Exemplary glass stabilization agents, including amorphous saccharides and buffers are described herein, as are suitable amounts of the glass stabilization agents. Suitable amounts of leucine and trileucine are provided throughout as well. As the final, dry powder formulation should contain the recited amounts of leucine, trileucine, histidine (and other components), such amounts are also used in the liquid feedstock. The result of the drying process following atomization is that any liquid solvent is removed, and thus the full amount of the original dry weight of the components corresponds to the final dry weight of the compounds in the dry powder formulation. Exemplary active agents are also described herein.

The methods and formulations described herein allow for the production of capsules, blister packs, etc., and other suitable containers for dry powder formulations. Such containers can be produced with 10-200 mg of dry powder, suitably 10-100 mg, 15-25 mg, or 20-75 mg, 20 mg or 50 mg or dry powder formulation. Such containers can suitably deliver 0.1-10 mg of a dry powder formulation to a patient's lungs.

In some instances, the use of the methods described herein provide pharmaceuticals that can reduce the total number of capsules required for use in an inhalation device. For example, the volume required to deliver 50-100 mg of active agent can be reduced from two larger 00 capsules to a single size 3 capsule.

Methods for producing an aerosol form of dry powder particles are known in the art and include for example, the use of inhaler devices such as a dry-powder inhaler (DPI) (e.g., a Monodose RS01 DPI by PLASTIAPE (Osnago, Italy)). The pharmaceutical compositions described herein can be dispensed into a gas stream by either a passive or an active inhalation device, and remain suspended in the gas for an amount of time sufficient for at least a portion of the microparticles to be inhaled by the patient, so that a portion of the microparticles reaches the lungs.

Anti-TSLP antibodies and antigen binding fragments thereof

The various methods, pharmaceutical compositions, unit doses disclosed herein utilize an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody. In some instances, the antigen binding fragment is a Fab.

- 5 The sequence of human TSLP polypeptide is provided below:

Met Phe Pro Phe Ala Leu Leu Tyr Val Leu Ser Val Ser Phe Arg Lys Ile Phe Ile Leu Gln Leu Val Gly Leu
Val Leu Thr Tyr Asp Phe Thr Asn Cys Asp Phe Glu Lys Ile Lys Ala Ala Tyr Leu Ser Thr Ile Ser Lys Asp
Leu Ile Thr Tyr Met Ser Gly Thr Lys Ser Thr Glu Phe Asn Asn Thr Val Ser Cys Ser Asn Arg Pro His Cys
Leu Thr Glu Ile Gln Ser Leu Thr Phe Asn Pro Thr Ala Gly Cys Ala Ser Leu Ala Lys Glu Met Phe Ala Met
10 Lys Thr Lys Ala Ala Leu Ala Ile Trp Cys Pro Gly Tyr Ser Glu Thr Gln Ile Asn Ala Thr Gln Ala Met Lys Lys
Arg Arg Lys Arg Lys Val Thr Thr Asn Lys Cys Leu Glu Gln Val Ser Gln Leu Gln Gly Leu Trp Arg Arg Phe
Asn Arg Pro Leu Leu Lys Gln Gln (SEQ ID NO: 27) The term "antibody" as used herein refers to a
tetrameric glycoprotein that consists of two heavy chains and two light chains, each comprising a variable
region and a constant region. "Heavy Chains" and "Light Chains" refer to substantially full-length
15 canonical immunoglobulin light and heavy chains (see e.g., Immunobiology, 5th Edition (Janeway and
Travers et al., Eds., 2001). The term "antibody" includes naturally occurring antibodies as well as all
recombinant forms of antibodies, e.g., humanized antibodies, fully human antibodies and chimeric
antibodies.

The term "antibody fragment" refers to a portion of an intact antibody. The terms "antigen-binding
20 fragment," "antigen-binding domain," or "antigen-binding region" of an antibody refers to a portion of an
intact antibody that binds to an antigen. Antigen-binding fragments of antibodies include, *inter alia*, Fab,
Fab', F(ab')₂, Fv, domain antibody (dAb), complementarity determining region (CDR) fragments, CDR-
grafted antibodies, single-chain antibodies (scFv), single chain antibody fragments, chimeric antibodies,
diabodies, triabodies, tetrabodies, minibody, linear antibody; chelating recombinant antibody, a tribody or
25 bibody, an intrabody, a nanobody, a small modular immunopharmaceutical (SMIP), an antigen-binding-
domain immunoglobulin fusion protein, single domain antibodies (including camelized antibody), a VHH
containing antibody, or a variant or a derivative thereof, and polypeptides that contain at least a portion of
an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as one,
two, three, four, five or six CDR sequences, as long as the antibody retains the desired biological activity.
30 In instances, the antigen-binding fragment of an antibody of the disclosure is selected from Fab, Fab',
F(ab')₂, scFv, minibody, or diabody. In certain instances, the antigen-binding fragment is a Fab. In some
instances, the antigen-binding fragment is of an IgG, IgM, IgA, IgD or IgE. In some instances, the anti-
TSLP antibody fragment is of an IgG1.

"Fab" refers to an antibody fragment comprising the VH-CH1 and VL-CL pairing. The term encompasses
35 Fabs comprising non-canonical sequence variants such as amino acid substitutions, deletions, or
insertions within the Fab outside of sequence regions typically associated with high sequence variability.
For example, Fab variants include Fabs comprising non-canonical amino acid or sequence changes in

- VH or VL framework regions or in the CH1 or CL domains. Such changes may include the presence of non-canonical cysteines or other derivatizable amino acids, which may be used to conjugate said Fab variants to heterologous moieties. Other such changes include the presence of non-canonical polypeptide linkers, which are polypeptide sequences that covalently bridge between two domains. For example, a
- 5 Fab variant may comprise a linker polypeptide that covalently attaches the CH1 domain to the VL domain, or the CL domain to the VH domain, such that the Fab can be expressed as a single polypeptide chain.

Light chain CDR (LCDR), light chain variable domain (VL), heavy chain CDR (HCDR) and heavy chain variable domain (VH) sequences of an exemplary Fab of the disclosure (herein termed FAB1) include those set out in Table 1 below.

- 10 **Table 1:** exemplary sequences of a Fab of the disclosure (herein termed FAB1).

SEQ ID NO	Description	Sequence
1	HCDR1 FAB1	Thr Tyr Gly Met His
2	HCDR2 FAB1	Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys Gly
3	HCDR3 FAB1	Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile
4	HEAVY CHAIN VH FAB1	Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
5	LCDR1 FAB1	Gly Gly Asn Asn Leu Gly Ser Lys Ser Val His
6	LCDR2 FAB1	Asp Asp Ser Asp Arg Pro Ser
7	LCDR3 FAB1	Gln Val Trp Asp Ser Ser Ser Asp His Val Val

8	LIGHT CHAIN VL FAB1	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
9	FAB1 VARIABLE HEAVY CHAIN VH (nucleic acid)	cagatgcagt tgggtgaatc tgggtggcggc gtggtgcagc ctggcagatc tctgagactg 60 tcttggtccg cctccggctt cacctcaga acctacggaa tgcactgggt ccgacaggcc 120 cctggcaaag gattggaatg ggtcgccgtg atttggtacg acggctccaa caagcactac 180 gccgactccg tgaagggcag attcaccatc accagagaca actccaagaa caccctgaac 240 ctgcagatga actccctgag agccgaggac accgccgtgt actattgtgc tagagcccct 300 cagtgggaac tcgtgcatga ggcctttgac atctggggcc agggaacaat ggtcaccgtc 360 tcctca 366
10	FAB1 VARIABLE LIGHT CHAIN VL (nucleic acid)	tcatatgttc ttacacaacc accgtcggtt tcggttgctc caggacaaac agctcgaatt 60 acatgcggag gaaacaacct cggatcgaag tcggttcaact ggtatcaaca aaagccagga 120 caagctccag ttctcgtggt gtacgatgat tcagatcgac catcatggat cccagagcga 180 ttctcaggat caaactcggg aaatactgcc acgctcaciaa ttacacgagg agaagcggga 240 gatgaagctg attactattg ccaagtgtgg gactcgtcgt cagatcatgt tgtttcggga 300 ggtggaacaa agctcacagt gctc 324
28	FAB1 HEAVY CHAIN (polypeptide)	Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys

29	FAB1 LIGHT CHAIN (polypeptide)	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
30	FAB1 HEAVY CHAIN (nucleic acid)	cagatgcagt tgggtgaatc tgggtggcgc gtggtgcagc ctggcagatc tctgagactg 60 tctgtgccg cctccggctt cacctcaga acctacggaa tgcactgggt ccgacaggcc 120 cctggcaaag gattggaatg ggtcgccgtg atttggtacg acggctcaa caagcactac 180 gccgactccg tgaagggcag attcaccatc accagagaca actccaagaa caccctgaac 240 ctgcagatga actccctgag agccgaggac accgccgtgt actattgtgc tagagccctt 300 cagtgggaac tcgtgcatga ggcctttgac atctggggcc aggaacaat ggtcaccgtc 360 tcctcagcct ccaccaaggg cccatcggtc tccccctgg caccctctc caagagcacc 420 tctgggggca cagcgccctt gggctgcctg gtcaaggact actccccga accggtgacg 480 gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca cctcccgcg tgctctacag 540 tcctcaggac tctactccct cagcagcgtg gtgacagtgc cctccagcag ctggggcacc 600 cagacctaca tctgaacgt gaatcacaag cccagcaaca ccaaggtgga caagagagtt 660 gagcccaaat cttgtgacaa a 681
31	FAB1 LIGHT CHAIN (nucleic acid)	tcatatgttc ttacacaacc accgtcggtt tcggttgctc caggacaaac agctcgaatt 60 acatgcggag gaaacaacct cggatcgaag tcggttcaat ggtatcaaca aaagccagga 120 caagctccag ttctcgtggt gtacgatgat tcagatcgac catcatggat ccagagcgga 180 ttctcaggat caaactcggg aaatactgcc acgctcaca tttcacgcgg agaagcggga 240 gatgaagctg attactattg ccaagtgtgg gactcgtcgt cagatcatgt tgttttcgga 300 ggtggaacaa agctcacagt gctcggtcag cccaaggctg cccctcggt cactctgttc 360 ccgccctct ctgaggagct tcaagccaac aaggccacac tgggtgtct cataagtac 420 tttaccggg gagccgtgac agtggcctgg aaggcagata gcagccccg caaggcgga 480

	gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg	540
	agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cagcatgaa	600
	gggagcaccg tggagaagac agtggcccct acagaatgtt ca	642

In certain instances, the antigen binding fragment within the composition comprises:

- a heavy chain variable domain comprising:
 - a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:1, a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:2, and
 - 5 a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:3, wherein either of heavy chain CDR1, 2 or 3 optionally comprises a single amino acid substitution, and
 - a light chain variable domain comprising:
 - a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO:5, a
 - 10 light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO:6, and a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:7; wherein either of light chain CDR 1, 2 or 3 optionally comprises a single amino acid substitution.

In certain instances, the antigen binding fragment within the composition comprises a heavy chain variable domain comprising a light chain CDR1 sequence having the amino acid sequence set forth in

15 SEQ ID NO:1, a heavy chain CDR2 sequence having the amino acid sequence set forth in SEQ ID NO:2, and a heavy chain CDR3 sequence having the amino acid sequence set forth in SEQ ID NO:3, and a light chain CDR1 sequence having the amino acid sequence set forth in SEQ ID NO:5, a light chain CDR2 sequence having the amino acid sequence set forth in SEQ ID NO:6, and a light chain CDR3 sequence having the amino acid sequence set forth in SEQ ID NO:7.

20 In additional instances, the antigen binding fragment for use in the pharmaceutical composition comprises a heavy chain variable domain that is a sequence of amino acids that is at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 4 and a light chain variable domain that is a sequence of amino acids that is at least 95%, 90%, 85% or 80% identical to, SEQ ID NO: 8.

In additional instances, the antigen binding fragment for use in the composition comprises (a) a heavy

25 chain variable domain that is a sequence of amino acids that is at least 95%, 90%, 85% or 80% identical to, SEQ ID NO: 4; or a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 30, (b) a light chain variable domain that is a sequence of amino acids that is at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 8; or a sequence of amino acids encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 31; or a heavy chain variable

30 domain of (a) and a light chain variable domain of (b).

In additional instances, the antigen binding fragment for use in the pharmaceutical composition comprises a heavy chain variable domain comprising SEQ ID NO:4; and a light chain variable domain comprising

SEQ ID NO:8. In additional instances, the antigen binding fragment for use in the pharmaceutical composition comprises a heavy chain comprising the sequence set forth in SEQ ID NO:28; and a light chain comprising the sequence set forth in SEQ ID NO:29.

- Further light chain CDR (LCDR), light chain variable domain (VL), heavy chain CDR (HCDR) and heavy chain variable domain (VH) sequences of antigen binding fragments of the disclosure include those set out in Table 2 below:

Table 2: exemplary sequences of a Fab of the disclosure (herein termed FAB2).

SEQ ID NO	Description	Sequence
11	LCDR1 FAB2	Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His
12	LIGHT CHAIN VL FAB2	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Ile Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
13	LCDR1 FAB3	Gly Gly Asn Asn Val Gly Ser Lys Ser Val His
14	LIGHT CHAIN VL FAB3	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Val Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
15	HCDR2 FAB4	Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Glu Ser Val Lys Gly
16	HEAVY CHAIN VH FAB4	Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser

17	HCDR2 FAB5	Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys Ala
18	HEAVY CHAIN VH FAB5	Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Thr Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val Lys Ala Arg Phe Thr Ile Thr Arg Asp Asn Ser Lys Asn Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ala Pro Gln Trp Glu Leu Val His Glu Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
19	LCDR1 FAB6	Gly Gly Gln Asn Leu Gly Ser Lys Ser Val His
20	LIGHT CHAIN VL FAB6	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Gln Asn Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
21	LCDR1 FAB7	Gly Gly Asn Gln Leu Gly Ser Lys Ser Val His
22	LIGHT CHAIN VL FAB7	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Gln Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
23	LCDR3 FAB8	Gln Val Trp Asp Thr Ser Ser Asp His Val Val
24	LIGHT CHAIN VL FAB8	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Thr Ser Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
25	LCDR3 FAB9	Gln Val Trp Asp Ser Thr Ser Asp His Val Val

26	LIGHT CHAIN VL FAB9	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Leu Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Val Tyr Asp Asp Ser Asp Arg Pro Ser Trp Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Gly Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Thr Ser Asp His Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
----	---------------------------	--

In certain instances, the heavy variable chain and the light variable chain domains of the antigen binding fragment of the disclosure comprise any of the combinations of CDR sequences set out in Table 3 below:

Table 3: CDR combinations for Fabs of the disclosure

	VH CDRs 1, 2 and 3	VL CDRs 1, 2 and 3
FAB1	SEQ ID NOS:1, 2 and 3	SEQ ID NOS:5, 6 and 7
Fab2	SEQ ID NOS:1, 2 and 3	SEQ ID NO:11, 6 and 7
Fab3	SEQ ID NOS:1, 2 and 3	SEQ ID NO:14, 6 and 7
Fab4	SEQ ID NO:1, 15 and 3	SEQ ID NOS:5, 6 and 7
Fab5	SEQ ID NOS: 1, 17 and 3	SEQ ID NOS:5, 6 and 7
Fab6	SEQ ID NOS:1, 2 and 3	SEQ ID NOS:19, 6 and 7
Fab7	SEQ ID NOS:1, 2 and 3	SEQ ID NOS:19, 6 and 7
Fab8	SEQ ID NOS:1, 2 and 3	SEQ ID NOS:5, 6 and 23
Fab9	SEQ ID NOS:1, 2 and 3	SEQ ID NOS:5, 6 and 25

- 5 In some instances, the antigen binding fragment for use in the pharmaceutical composition may be derived from one of those described WO2023098491A1, WO2021155634A1, WO2022166072A1, WO2021043221A1, WO2022184074A1, WO2021104053A1, WO2023116925A1, WO2021155861A1, WO2022116858A1, WO2022117079A1, WO2020244544A1, WO2021152488A1, WO2022253147A1, WO2023070948A1, WO2023142309A1, WO2022095689A1, WO2021115240A1, WO2022166739A1 and
- 10 WO2019100111A1, the disclosure of each of which is incorporated by reference herein.

In some instances, the antigen binding fragment for use in the pharmaceutical composition may be derived from one of those set out in the Table 4 below (which includes sequence identifiers from the listed publications themselves):

Table 4: alternative anti-TSLP antibodies that could be used in the formulations disclosed herein.

WO2017/042701	An anti-TSLP antibody comprising a heavy chain (HC) CDR1 comprising the sequence of SEQ ID NO: 13, a HC CDR2 comprising the sequence of SEQ ID NO: 14, and a HC CDR3 comprising the sequence of SEQ ID NO: 15; An anti-TSLP antibody comprising a light chain (LC) CDR1 comprising the sequence of SEQ ID NO: 16, a LC CDR2 comprising the sequence of SEQ ID NO: 17, a LC CDR3 comprising the sequence of SEQ ID NO: 18; An anti-TSLP antibody comprising a heavy chain (HC) CDR1 comprising the sequence of SEQ ID NO: 19, a HC CDR2 comprising the sequence of SEQ ID NO: 20, a HC CDR3 comprising the sequence of SEQ ID NO:15; An anti-TSLP antibody comprising a light chain (LC) CDR1 comprising the sequence of SEQ ID NO: 21, a LC CDR2 comprising the sequence of SEQ ID NO: 22, a LC CDR3 comprising the sequence of SEQ ID NO: 23; An anti-TSLP antibody comprising a HC variable region comprising the sequence of SEQ ID NO: 26 and/or a LC variable region comprising the sequence of SEQ ID NO: 27; An anti-TSLP antibody comprising a HC variable region comprising the sequence of SEQ ID NO: 28 and/or a LC variable region comprising the sequence of SEQ ID NO: 29; An anti-TSLP antibody that comprises a paratope comprising at least one of the following residues: Thr28, Asp31, Tyr32, Trp33, Asp56, Glu101, Ile102, Tyr103, Tyr104, Tyr105 of a heavy chain sequence of SEQ ID NO: 26 or Gly28, Ser29, Lys30, Tyr31, Tyr48, Asp50, Asn51, Glu52, Asn65, and Trp92 of a light chain sequence of SEQ ID NO:27; An anti-TSLP antibody that specifically binds an epitope in human TSLP, wherein the epitope comprises at least one of the following residues: Lys38, Ala41, Leu44, Ser45, Thr46, Ser48, Lys49, Ile52, Thr53, Ser56, Gly57, Thr58, Lys59, Lys101, Gln145, and Arg149 of SEQ ID NO: 30;
WO2016/142426	An anti-TSLP antibody comprising the amino acid sequence of SEQ ID NO: 31;

	An anti-TSLP antibody comprising a CDR1 comprising the sequence of SEQ ID NO: 32; a CDR2 comprising the sequence of SEQ ID NO: 33, and a CDR3 comprising the sequence of SEQ ID NO: 34; An anti-TSLP antibody comprising a CDR1 comprising the sequence of SEQ ID NO: 32; a CDR2 comprising the sequence of SEQ ID NO: 35, and a CDR3 comprising the sequence of SEQ ID NO: 34; An anti-TSLP antibody comprising a variant of the CDR1 of SEQ ID NO: 31 wherein the residue corresponding to residue 28 in SEQ ID NO:31 is Pro, the residue corresponding to residue 30 in SEQ ID NO:31 is Arg, the residue corresponding to residue 31 in SEQ ID NO:31 is Asn, the residue corresponding to residue 32 in SEQ ID NO: 31 is Trp and the residue corresponding to residue 34 in SEQ ID NO: 31 is Asp; An anti-TSLP antibody comprising a variant of the CDR2 of SEQ ID NO: 31 wherein the residue corresponding to residue 50 in SEQ ID NO:31 is Gly, the residue corresponding to residue 53 in SEQ ID NO:31 is His and the residue corresponding to residue 55 in SEQ ID NO:31 is Gln; An anti-TSLP antibody comprising a variant of the CDR3 of SEQ ID NO: 31 wherein the residue corresponding to residue 91 in SEQ ID NO:31 is He, Leu, Val or Phe, the residue corresponding to residue 92 in SEQ ID NO:31 is Gly or Ala, the residue corresponding to residue 93 in SEQ ID NO:31 is Glu, Phe, Asp or Ser and the residue corresponding to residue 94 in SEQ ID NO:31 is Asp.
WO2010/017468	An anti-TSLP antibody (9B7) comprising a HC CDR3 comprising the sequence of SEQ ID NO:38, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 36, 37, and 39-41; An anti-TSLP antibody (6C5) comprising a HC CDR3 comprising the sequence of SEQ ID NO:44, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 42, 43, and 45-47; An anti-TSLP antibody (6A3) comprising a HC CDR3 comprising the sequence of SEQ ID NO:50, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 48, 49, and 51-53; An anti-TSLP antibody (1A11) comprising a HC CDR3 comprising the sequence of SEQ ID NO:56, wherein the other CDRs of the HC and LC comprise the sequences of SEQ ID NOs: 54, 55, and 57-59; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO:60 and/or the light chain variable region of SEQ ID NO:61;

	An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 62 and/or the light chain variable region of SEQ ID NO:63; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 64 and/or the light chain variable region of SEQ ID NO:65; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO:66 and/or the light chain variable region of SEQ ID NO: 67; An anti-TSLP antibody comprising (i) heavy chain variable region of SEQ ID NO: 68 and/or the light chain variable region of SEQ ID NO: 69; An anti-TSLP antibody comprising a HC CDR selected from the group consisting of SEQ ID NO:38, SEQ ID NO:44, SEQ ID NO:50 and SEQ ID NO:56, and analogs thereof; An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CDRH1: RYNVH (SEQ ID NO:36) [referred to herein as "SEQ ID NO: 32"], CDRH2: MIWDGGSTDYNSALKS (SEQ ID NO:37) [referred to herein as "SEQ ID NO: 33"], CDRH3: NRYESG (SEQ ID NO:38) [referred to herein as "SEQ ID NO: 34"], and a light chain comprising the following CDRs or analogs thereof CDRL1: KSSQSLLNSGSRKNYLT (SEQ ID NO:39) [referred to herein as "SEQ ID NO: 35"], CDRL2: WASTRES (SEQ ID NO:40) [referred to herein as "SEQ ID NO: 36"] , and CDRL3: QNDYTYPFTFGS (SEQ ID NO:41) [referred to herein as "SEQ ID NO: 37"]; or An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CRDH1: AYWMS (SEQ ID NO:42) [referred to herein as "SEQ ID NO: 38"], CDRH2: EINPDSSTINCTPSLKD (SEQ ID NO:43) [referred to herein as "SEQ ID NO: 39"], CDRH3: RLRFWYFDVW (SEQ ID NO:44) [referred to herein as "SEQ ID NO: 40"], and a light chain comprising the following CDRs or analogs thereof CDRL1: RSSQSIVQSNGNTYLE (SEQ ID NO:45) [referred to herein as "SEQ ID NO: 41"], CDRL2: KVSNRFS (SEQ ID NO:46) [referred to herein as "SEQ ID NO: 42"], and CDRL3: FQGSHVPRT (SEQ ID NO:47) [referred to herein as "SEQ ID NO: 43"]; An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CRDH1: TDYAWN (SEQ ID NO:48) [referred to herein as "SEQ ID NO: 44"], CDRH2: YIFYSGSTTYTPSLKS (SEQ ID NO:49) [referred to herein as "SEQ ID NO: 45"], CDRH3: GGYDVNYF (SEQ ID NO:50) [referred to herein as "SEQ ID NO: 46"], and a light chain comprising the following CDRs or analogs thereof
--	--

	CDRL1: LASQTIGAWLA (SEQ ID NO:51) [referred to herein as "SEQ ID NO: 47"], CDRL2: AATRLAD (SEQ ID NO:52) [referred to herein as "SEQ ID NO: 48"], and CDRL3: QQFFSTPWT (SEQ ID NO:53) [referred to herein as "SEQ ID NO: 49"]; An anti-TSLP antibody comprising a heavy chain comprising the following CDRs or analogs thereof CDRH1: GYTMN (SEQ ID NO:54) [referred to herein as "SEQ ID NO: 50"], CDRH2: LINPYNGVTSYNQKFK [referred to herein as "SEQ ID NO: 51"] (SEQ ID NO:55), CDRH3: GDGNYWYF (SEQ ID NO:56) [referred to herein as "SEQ ID NO: 52"], and a light chain comprising the following CDRs or analogs thereof CDRL1: SASSSVTYMHW (SEQ ID NO:57) [referred to herein as "SEQ ID NO: 53"], CDRL2: EISKLAS (SEQ ID NO:58) [referred to herein as "SEQ ID NO: 54"], and CDRL3: QEWNYPYTF (SEQ ID NO:59) [referred to herein as "SEQ ID NO: 55"]; An anti-TSLP antibody comprising a HC CDR1 comprising the sequence of SEQ ID NO: 70; a CDR2 comprising the sequence of SEQ ID NO: 71, and a CDR3 comprising the sequence of SEQ ID NO: 72; An anti-TSLP antibody comprising a LC CDR1 comprising the sequence of SEQ ID NO: 73; a CDR2 comprising the sequence of SEQ ID NO: 74, and a CDR3 comprising the sequence of SEQ ID NO: 75;
US2012/0020988	An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:77, and CDR3 region of SEQ ID NO:78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 79, a CDR2 region of SEQ ID NO:80, and a CDR3 region of SEQ ID NO:81. An anti-TSLP antibody comprising a heavy chain variable domain comprising SEQ ID NO:82 and a light chain variable domain comprising SEQ ID NO:83; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76 or 84, a CDR2 region of SEQ ID NO: 77 or 85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 79 or 86, a CDR2 region of SEQ ID NO: 80, 87, or 88, and a CDR3 region of SEQ ID NO: 81. An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable

	domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:87 and a CDR3 region of SEQ ID NO:81; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:88 and a CDR3 region of SEQ ID NO:81; An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 84, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO:88 and a CDR3 region of SEQ ID NO:81; or An anti-TSLP antibody comprising a heavy chain variable domain comprising a CDR1 region of SEQ ID NO: 76, a CDR2 region of SEQ ID NO:85, and CDR3 region of SEQ ID NO: 78, and a light chain variable domain comprising a CDR1 region of SEQ ID NO: 86, a CDR2 region of SEQ ID NO: 80 and a CDR3 region of SEQ ID NO:81. An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:90; An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:91; An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:92 and a light chain variable domain comprises SEQ ID NO:93; An anti-TSLP antibody comprising a heavy chain variable domain comprises SEQ ID NO:89 and a light chain variable domain comprises SEQ ID NO:94,
US8637019	An anti-TSLP antibody comprising heavy chain variable region comprising: a CDR-H1 sequence comprising SEQ ID NO:95, a CDR-H2 sequence comprising SEQ ID NO:96, and a CDR-H3 sequence comprising SEQ ID NO:97; and/or an antibody light chain variable region or a TSLP-binding fragment thereof, said light chain variable region comprising: a CDR-L1 sequence comprising SEQ ID NO: 98, a CDR-L2 sequence comprising SEQ ID NO: 99, and a CDR-L3 sequence comprising SEQ ID NO: 100.

	An anti-TSLP antibody comprising a heavy chain variable region comprises the amino acid sequence of SEQ ID NO:101 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 102. An anti-TSLP antibody comprising SEQ ID NO:103 and SEQ ID NO:104.
WO2020244544	An anti-TSLP antibody comprising a heavy chain variable region and a light chain variable region, wherein: the heavy chain variable region comprises HCDR1, HCDR2 and HCDR3 as shown in SEQ ID NO: 26, SEQ ID NO: 94 and SEQ ID NO: 28, respectively, and the light chain variable region comprises LCDR1, LCDR2 and LCDR3 as shown in SEQ ID NO: 29, SEQ ID NO: 113 and SEQ ID NO: 31, respectively.

Methods of Treatment

Also provided herein are methods of treatment comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition described herein. In some instances, the method is for the treatment of a TSLP-related condition.

"Treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

"Therapeutically effective amount" refers to an amount of an antigen binding fragment of an anti-TSLP antibody disclosed herein or other drug effective to "treat" a disease or disorder in a subject or mammal.

"Subject" or "individual" or "animal" or "patient" or "mammal," is means any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired, except where the subject is defined as a 'healthy subject'. Mammalian subjects include humans; domestic animals; farm animals; such as dogs, cats, guinea pigs, rabbits, rats, mice, horses, cattle, cows, and so on. Preferably the subject is human. The patient may be an adult, or a child or adolescent.

Also provided herein are pharmaceutical compositions for use in therapy. In some instances, the therapy is the treatment of a TSLP-related condition.

Also provided herein is the use of the antigen binding fragment of an anti-TSLP antibody or pharmaceutical compositions comprising the same in the manufacture of a medicament for use in the treatment of a disease. In some instances, the disease is a TSLP-related condition.

5 The disclosure also provides for the use of the antigen binding fragment of an anti-TSLP antibody or pharmaceutical compositions comprising the same in therapy. In some instances, the therapy is the treatment of a TSLP-related condition.

Within this section of the description any reference to a method of treatment shall be construed to disclose the corresponding instances of uses or pharmaceutical compositions for use.

10 In some instances, the TSLP-related condition is a TSLP-related inflammatory condition. In some instances, the TSLP-related inflammatory condition is selected from asthma, sepsis, septic shock, atopic dermatitis, allergic rhinitis, allergic rhinosinusitis, allergic conjunctivitis, eosinophilic esophagitis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), asthma, COPD overlap syndrome (ACOS), chronic bronchitis, emphysema, chronic rhinosinusitis with or without nasal polyps, vasculitis, GvHD, uveitis, chronic idiopathic urticaria, sinusitis or pancreatitis.

15 In some instances, the TSLP-related condition is asthma.

In some instances, the TSLP-related condition is COPD.

In some instances, the asthma is moderate or severe asthma, or moderate-to-severe asthma. In some instances, the subject having moderate or severe asthma, or moderate-to-severe asthma, may mean the subject has a diagnosis of moderate or severe asthma, or moderate-to-severe asthma. In some
20 instances, the subject may have a documented history of moderate or severe asthma, or moderate-to-severe asthma for at least 1 year.

Asthma is a chronic inflammatory disease of the airways affecting 1-18% of the population in different countries and is characterized by bronchial hyperreactivity and reversible airflow limitation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough. The
25 etiology of asthma is thought to be multi-factorial and there are recognizable clusters of demographic, clinical and/or pathophysiological phenotypes. In patients with more severe phenotypes, some phenotype-guided treatments are available. However, no strong relationship between pathological symptoms and clinical presentations and response to therapies have been established.

Asthma may be diagnosed or assessed by a number of different measures, including:

30 Airway inflammation evaluated using a standardized single-breath Fraction of Exhaled Nitric Oxide (FeNO) (ATS, Am J Respir Crit Care Med. 171(8):912-30, 2005). FeNO has not been established for confirming asthma diagnosis but elevated FeNO has been associated with asthma characterized by a Type 2 airway inflammation.

Determining the atopic status. This can be identified by a skin prick test with common environmental
35 allergens or by measuring the level of specific IgE in serum. As with FeNO, allergy tests do not rule in or rule out a diagnosis of asthma but the presence of atopy increases the probability that a patient with respiratory symptoms has allergic asthma.

Bronchial provocation testing. These tests monitor variable airflow limitation to assess airway hyperresponsiveness (AHR). Subjects can be challenged with chemical agents such as methacholine. Such tests are moderately sensitive to the diagnosis of asthma.

5 The term "FENO" refers to fractional exhaled nitric oxide, which is a biomarker for bronchial or airway inflammation. FENO is produced by airway epithelial cells in response to inflammatory cytokines, such as TSLP, IL-4 and IL-13. FENO levels in healthy adults range from 2 to 30 parts per billion (ppb). An exemplary assay for measuring FENO comprises subjects inhaling to total lung capacity through the NIOX MINO® Airway Inflammation Monitor and then exhaling for 10 seconds at 50 ml/sec (assisted by visual and auditory cues).

10 Different asthma subtypes have been identified, including allergic asthma, non-allergic asthma, late-onset asthma (which typically tends to be non-allergic), asthma with persistent airflow limitation (which is linked to airway wall remodeling, leading to a long-standing, persistent, irreversible airflow limitation), and asthma with obesity (which is typically linked to a non/low eosinophilic mechanism of action). In some instances, subjects treated by the present disclosure may have any type or origin of asthma.

15 There are different levels of asthma severity, which are currently assessed retrospectively from the level of treatment required to control symptoms and exacerbations. The severity index comprises three main groups: mild asthma, moderate asthma, and severe asthma. Severity of asthma is defined on the GINA scale by the level of treatment required to gain adequate control of symptoms. The GINA scale is defined in the "Pocket Guide for Asthma Management and Prevention," Global Initiative for Asthma; 2019. Unless
20 otherwise stated herein, references to "moderate asthma" or "severe asthma" are in accordance with the definitions on the GINA scale. For instance, moderate asthma refers to asthma that has a Global Initiative for Asthma (GINA) scale of 3 or less, suitably a GINA scale of 2 or 3 (i.e. GINA step 2 or step 3), and severe asthma refers to asthma that requires high intensity treatment (e.g., GINA Step 4 and Step 5) to maintain good control, or where good control is not achieved despite high intensity treatment (GINA,
25 Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA) December 2012).

In some instances, the subject has a history of ≥ 1 or ≥ 2 severe exacerbation(s) within the last 12 months prior to the treatment. Severe exacerbations are defined as those episodes that lead to hospitalisation, emergency room visit, and/or treatment with oral glucocorticosteroid as detailed below:

30 Inpatient hospitalization: an admission to an inpatient facility and/or evaluation and treatment in healthcare facility for ≥ 24 hours due to asthma;

Emergency room or urgent care visit: evaluation and treatment for < 24 hours in an emergency department or urgent care centre due to asthma required systemic corticosteroids; and/or

35 Use of a temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.

In some instances, the asthma moderate asthma, severe asthma, or moderate-to-severe asthma. In some instances, the asthma is not well-controlled on controller or reliever standard of care therapies defined in steps 1 and 2 of the GINA scale. In some instances, therefore the asthma to be treated by the present disclosure may have uncontrolled asthma. In some instances, the asthma is moderate asthma
5 uncontrolled on standard of care therapy, severe asthma uncontrolled on standard of care therapy, or moderate-to-severe asthma uncontrolled on standard of care therapy. Standard of care (SOC) therapy is as defined in the GINA scale.

Chronic obstructive pulmonary disease (COPD) is a progressive disease and a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in
10 prevalence and is projected to be the third leading cause of death and disability worldwide by 2020.

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. In addition to a substantial economic burden, AECOPDs are also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD show associated increased airway inflammation and accelerated decline in lung function compared with patients with infrequent
15 exacerbations.

In some instances, the subject has a baseline blood eosinophil count of ≥ 150 cells/ μ l or ≥ 300 cells/ μ l. In some instances, baseline refers to the blood eosinophil count prior to commencement of the treatment, e.g. within one month of the commencement of treatment.

In certain instances, the methods disclosed herein improve lung function in a subject with asthma. In some instances, the improving lung function means one or more of the following: improvement compared
20 to baseline of pre-bronchodilator (BD) FVC, post-BD-FVC, pre-BD-FEV₁, post-BD FEV₁, mean morning PEF or mean evening PEF.

In some instances, the improvement means achieving the minimal clinical important difference (MCID) for each of pre-bronchodilator (BD) FVC, post-BD-FVC, pre-BD-FEV₁, post-BD FEV₁, mean morning PEF or mean evening PEF, respectively.
25

The phrase "minimal clinically important difference" or "MCID" means that smallest change in a treatment outcome that an individual patient would identify as important and which would indicate a change in the patient's management. Some MCIDs are experimentally validated and others are study specific.

The term "pre-BD FEV₁", "preBD FEV₁" or "pre-bronchodilator (BD) FEV₁" refers to pre-bronchodilator forced expiratory volume 1. This is a measurement of forced expiratory volume of a subject in 1 second before administration of bronchodilator. In some instances, the minimum clinical important difference for pre-BD-FEV₁ is 100 ml.
30

In some instances, the increase in pre-BD-FEV₁ compared to baseline (e.g. the pre-BD-FEV₁ value prior to commencement of treatment) is at least 5 ml, at least 10 ml, at least 15 ml, at least 20 ml, at least 25
35 ml, at least 30 ml, at least 35 ml, at least 40 ml, at least 45 ml, at least 50 ml, at least 55 ml, at least 60 ml, at least 65 ml, at least 70 ml, at least 75 ml, at least 80 ml, at least 85 ml, at least 90 ml, at least 95 ml, at least 100 ml, at least 105 ml, at least 110 ml, at least 115 ml, at least 120 ml, at least 125 ml, at least 130 ml, at least 135 ml, at least 140 ml, at least 145 ml, at least 150 ml, at least 160 ml, at least 170

ml, at least 180 ml, at least 190 ml, at least 200 ml, at least 210 ml, at least 220 ml, at least 230 ml, at least 240 ml or at least 250 ml. In some instances, the increase in pre-BD-FEV₁ compared to baseline (e.g. the pre-BD-FEV₁ value prior to commencement of treatment) is at least 80 ml at day 2 after commencement of treatment, at least 45 ml or at least 100 ml at day 7 after commencement of treatment, at least 100 ml at day 14 after commencement of treatment, or at least 5 ml or at least 100 ml at day 28 after commencement of treatment.

The term "postBD-FEV₁" or "post-bronchodilator (BD)-FEV₁" refers to post-bronchodilator forced expiratory volume 1. This is a measurement of forced expiratory volume of a subject in 1 second after administration of bronchodilator.

10 The term "pre-BD-FVC" or "pre-bronchodilator (BD) forced vital capacity (FVC)" refers to bronchodilator Forced vital capacity. This is the total amount of air exhaled by a subject during a forced expiratory volume test or FVC test before administration of bronchodilator.

The term "post-BD-FVC" or "post-bronchodilator (BD)-FVC" refers to post-bronchodilator forced vital capacity. This is the total amount of air exhaled by a subject during a forced expiratory volume test or FVC test after administration of bronchodilator.

15 The term "bronchodilator" is a substance which dilates the bronchi and bronchioles, decreasing resistance in the respiratory airways and increasing airflow to the lungs. Suitable bronchodilators include a short-acting beta agonist (SABA) such as albuterol (90 1-1g metered dose) or salbutamol (1 00 1-1g metered dose) or equivalent (Sorkness et al, J Appl Physiol. 1 04(2):394-403, 2008).

20 The term "peak expiratory flow rate (PEF)" indicates the fastest rate that a subject can force air out of the lungs during a forced expiratory volume test or FVC test, typically measured in Litres/minute.

The term "forced expiratory volume (FEV)" is the amount of air expired by a subject during the first, second, and third seconds of the FVC test. The term FEV₁ as explained above is the amount of air expired by a subject during the first second of the FVC test.

25 The term "forced vital capacity" (FVC) or the forced vital capacity test is a measurement of the total amount of air exhaled forcefully and quickly by a subject after inhaling as much as possible.

In some instances, pre-BD-FEV₁, post-BD-FEV₁, pre-BD-FVC, post-BD-FVC Spirometry is performed according to ATS/European Respiratory Society (ERS) guidelines (Miller et al, Eur Respir J. 26(1):153-61, 2005). For example, multiple forced expiratory efforts (at least 3 but no more than 8) is performed at each spirometry session and the 2 best efforts that meet ATS/ERS acceptability and reproducibility criteria are recorded. The best efforts will be based on the highest FEV₁. The maximum fluvial exhalation volume (FEV₁) of the 2 best efforts will be used for the analysis. Both the absolute measurement (for FEV₁ and forced vital capacity (FVC)) and the percentage of predicted normal value will be recorded using appropriate reference values. The highest FVC will be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV₁).

Post-bronchodilator (Post-BD) spirometry testing is assessed after the subject has performed pre-BD spirometry. Pre-BD FEV₁ is measured as defined above using spirometry before administration of a

suitable bronchodilator to the subject. To measure post-BD FEV₁, maximal bronchodilation is induced using a short-acting beta agonist (SABA) such as albuterol (90 1-1g metered dose) or salbutamol (1 00 1-1g metered dose) or equivalent with a spacer device for a maximum of 8 total puffs (Sorkness et al, J Appl Physiol. 1 04(2):394-403, 2008). The highest pre- and post-BD FEV₁ obtained after 4, 6, or 8 puffs is used to determine reversibility and for analysis. Reversibility algorithm is as follows: %Reversibility= (post-BD FEV₁- pre-BD FEV₁) x 1 00/pre-BD FEV₁

The Ph1b portion of the study Investigating the Safety, Tolerability and Effects of FAB1 in Healthy Subjects and Subjects With Asthma on Inhaled Corticosteroids and Long-acting Beta-agonists (NCT05110976) demonstrated that FAB1 resulted in numerical improvements in lung function (namely pre-BD FEV₁), as shown in Figure 26. Accordingly, in some instances, the methods disclosed herein improves pre-BD-FEV₁ in a subject with a TSLP-related condition, such as asthma.

In some instances, the improvement in lung function is within 0.5 h of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 1 h of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 6 h of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 24 h of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 7 days of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 14 days of first dose with the composition disclosed herein. In some instances, the improvement in lung function is within 28 days of first dose with the composition disclosed herein. Figure 26B shows that subjects in part B of NCT05110976 who were administered 8 mg FAB1 displayed a trend towards an improvement in pre-BD FEV₁ in the high dose arm, with 105ml increase at day 28, and early effects seen at 6 hours after first dose.

In some instances, the methods disclosed herein improve symptoms of asthma in a subject. In some instances, improving symptoms of asthma means one or more of the following: improvement compared to baseline mean asthma symptom diary score, ACQ-6 score, AQLQ score, or SGRQ score.

Asthma Control Questionnaire (ACQ) 6

The Asthma Control Questionnaire (ACQ) 6 is a patient-reported questionnaire assessing asthma symptoms (i.e., night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use and FEV₁ (Juniper et al, Oct 1999). The ACQ-6 is a shortened version of the ACQ that omits the FEV₁ measurement from the original ACQ score. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of 0.75 indicate well-controlled asthma, scores between 0.75 and 1.5 indicate partly-controlled asthma, and a score > 1.5 indicates uncontrolled asthma (Juniper et al, Respir Med. 1 00(4):616-21, 2006). Individual changes of at least 0.5 are considered to be clinically meaningful (Juniper et al, Respir Med. 99(5):553-8, 2005). Accordingly, in some instances, the minimum clinical important difference for ACQ-6 is 0.5.

In some instances, the disclosure provides methods for improving lung function, wherein the method results in a 0.5 point improvement in ACQ-6 score compared to baseline.

Standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 (or "AQLQ") is a questionnaire that measures the health-related quality of life experienced by asthma subjects. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Subjects are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline. Accordingly, in some instances, the minimum clinical important difference for AQLQ is 0.5.

In some instances, the disclosure provides methods for improving lung function, wherein the method results in a 0.5 point improvement in AQLQ compared to baseline.

St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with a minimum clinically important difference (MCID). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009). SGRQ is a qualified biomarker and the responder definition is generally a 4 point improvement from baseline. Accordingly, in some instances, the minimum clinical important difference for SGRQ is 4.

In some instances, the disclosure provides methods for improving lung function, wherein the method results in a 4 point improvement in SGRQ score compared to baseline.

In some instances, the improvement in asthma symptoms is within 7 days of first dose with the composition disclosed herein. In some instances, the improvement in asthma symptoms is within 14 days of first dose with the composition disclosed herein. In some instances, the improvement in asthma symptoms is within 28 days of first dose with the composition disclosed herein. Figure 27 shows that subjects in part B of NCT05110976 who were administered 8 mg FAB1 displayed a trend towards an improvement in ACQ-6 score as evidenced by mean change from baseline over time in the high dose arm (8 mg).

Composite Exacerbation (CompEx) event rate

The CompEx Asthma is a composite endpoint that allows evaluation of treatment effect on exacerbation involving fewer participants compared with severe exacerbations. There are two main types of CompEx Asthma events:

- 5 • Severe exacerbations of asthma
- Diary-based (objective deterioration)

The CompEx for asthma is described in more detail in the Example 8.

In some aspects, the disclosure provides a method for improving time to first CompEx event in a subject with asthma.

- 10 In another aspect the disclosure provides a method for improving lung function in a subject with asthma, wherein the improvement in lung function comprised an improved in time to first CompEx event compared to placebo.

- In another aspect the disclosure provides a method for improving lung function in a subject with asthma, wherein the improvement in lung function comprised an improved in time to first CompEx event. In some instances, the improved time is compared to placebo. In some instances, the improved time is compared to baseline. In some instances, baseline is the time to first CompEx event in a subject who has not received the treatment described herein. As described herein, the ability to deliver the antigen binding fragment of the anti-TSLP antibody via inhalation provides a delivery mechanism more amenable to use in a primary care setting. Accordingly, the pharmaceutical composition described herein may be administered by inhalation or intranasally. Accordingly, in some instances the pharmaceutical composition described herein may be an inhalable pharmaceutical composition. In some instances, the pharmaceutical composition is administered by dry powder inhaler.
- 15 In some instances, the improved time is compared to placebo. In some instances, the improved time is compared to baseline. In some instances, baseline is the time to first CompEx event in a subject who has not received the treatment described herein. As described herein, the ability to deliver the antigen binding fragment of the anti-TSLP antibody via inhalation provides a delivery mechanism more amenable to use in a primary care setting. Accordingly, the pharmaceutical composition described herein may be administered by inhalation or intranasally. Accordingly, in some instances the pharmaceutical composition described herein may be an inhalable pharmaceutical composition. In some instances, the pharmaceutical composition is administered by dry powder inhaler.
- 20 In some instances, the improved time is compared to placebo. In some instances, the improved time is compared to baseline. In some instances, baseline is the time to first CompEx event in a subject who has not received the treatment described herein. As described herein, the ability to deliver the antigen binding fragment of the anti-TSLP antibody via inhalation provides a delivery mechanism more amenable to use in a primary care setting. Accordingly, the pharmaceutical composition described herein may be administered by inhalation or intranasally. Accordingly, in some instances the pharmaceutical composition described herein may be an inhalable pharmaceutical composition. In some instances, the pharmaceutical composition is administered by dry powder inhaler.

- In instances of the methods of treating asthma, the composition is administered frequently and at lower dosages than a systemically administered anti-TSLP medicine. In some instances, the formulation may be administered daily. Such instances may be more convenient for the subject or patient. Furthermore, such instances may reduce side effects that can occur via systemic administration.
- 25 In instances of the methods of treating asthma, the composition is administered frequently and at lower dosages than a systemically administered anti-TSLP medicine. In some instances, the formulation may be administered daily. Such instances may be more convenient for the subject or patient. Furthermore, such instances may reduce side effects that can occur via systemic administration.

- In some instances, the anti-drug antibody (ADA) prevalence in the subject following treatment with the pharmaceutical composition or the dry powder formulation disclosed herein is less than 6%, less than 5% or less than 4% and/or the ADA incidence is less than 4%, less than 3% or less than 2%. ADA prevalence is the percentage of ADA-evaluable participants who were ADA+ at any time, while ADA incidence is the percentage of ADA-evaluable participants who had treatment emergent anti-drug antibodies (TE-ADA+).
- 30 In some instances, the anti-drug antibody (ADA) prevalence in the subject following treatment with the pharmaceutical composition or the dry powder formulation disclosed herein is less than 6%, less than 5% or less than 4% and/or the ADA incidence is less than 4%, less than 3% or less than 2%. ADA prevalence is the percentage of ADA-evaluable participants who were ADA+ at any time, while ADA incidence is the percentage of ADA-evaluable participants who had treatment emergent anti-drug antibodies (TE-ADA+).

- In some instances, the compositions provide for the possibility of treating patients with moderate-severe asthma who could be managed in a primary care setting, or for treating patients with moderate-severe asthma with poor access to treatment via specialist care. For example, the compositions may be useful for the treatment of moderate-severe asthma patients with a Global Initiative for Asthma (GINA) scale of 4-5. Suitably, the compositions provide for the possibility of treating moderate-severe asthma that is uncontrolled. Suitably, the compositions provide for the possibility of treating moderate-severe asthma
- 35 In some instances, the compositions provide for the possibility of treating patients with moderate-severe asthma who could be managed in a primary care setting, or for treating patients with moderate-severe asthma with poor access to treatment via specialist care. For example, the compositions may be useful for the treatment of moderate-severe asthma patients with a Global Initiative for Asthma (GINA) scale of 4-5. Suitably, the compositions provide for the possibility of treating moderate-severe asthma that is uncontrolled. Suitably, the compositions provide for the possibility of treating moderate-severe asthma

that is uncontrolled on medium dose to high dose ICS:LABA with one or more exacerbations and frequent symptoms.

The pharmaceutical composition disclosed herein may be administered in combination with any known therapy for asthma and/or COPD, including any agent or combination of agents that are known to be useful, or which have been used or are currently in use, for treatment of inflammatory diseases, e.g. asthma or COPD. Exemplary active agents that can be administered in combination with the composition described herein include, but are not limited to, inhaled corticosteroids (ICS), bronchodilators (including long-acting beta agonists (LABA), long-acting anti-muscarinic agonists (LAMA), short-acting beta agonist (SABA), and muscarinic β_2 -agonists (MABA)), antihistamines, antileukotrienes, PDE-4 inhibitors, janus kinase inhibitors and phosphoinositide 3-kinase inhibitors.

Thus, in some instances, the subject to be or being treated is co-administered a background therapy. In some instances, the subject is already receiving the background therapy prior to the treatment. In some instances, the background therapy is selected from: inhaled corticosteroids, Leukotriene modifiers, long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), combination therapies such as Fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol and fluticasone and vilanterol, theophylline, short-acting beta agonists (SABAs), ipratropium or a combination of ipratropium and albuterol or oral corticosteroids. In some instances, the background therapy comprises medium or high dose ICS (as per GINA 2023 report) in combination with LABA (GINA step 4 or 5 therapy).

The term "combination" refers to either a fixed combination in one dosage unit form, or a combined administration where a pharmaceutical composition as described herein and a combination partner (e.g. another drug, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term "fixed combination" means that the therapeutic agents, e.g. an anti-TSLP Fab and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the therapeutic agents, e.g., an anti-TSLP Fab and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more therapeutic agent.

The term "combination therapy" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (e.g., tablets, capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner, either at approximately the same time or at different times. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

In some instances, the pharmaceutical composition may be administered to a human or other animal in accordance with the aforementioned methods of treatment/medical uses in an amount sufficient to produce a therapeutic effect.

In some instances, the pharmaceutical composition can be administered to such human or other animal in a conventional dosage form prepared by combining the anti-TSLP Fab with a conventional pharmaceutically acceptable carrier or diluent according to known techniques.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

In some instances, the pharmaceutical compositions are formulated to comprise a pharmaceutically acceptable, non-toxic, sterile carrier such as physiological saline, non-toxic buffers, preservatives and the like. In some instances, the pharmaceutical composition may include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Suitable formulations for use in the therapeutic methods disclosed herein are described in Remington's Pharmaceutical Sciences (Mack Publishing Co.) 16th ed. (1980).

In some instances, the components as recited herein for preparing said pharmaceutical composition may be packaged and sold in the form of a kit. Such a kit will in some instances have labels or package inserts indicating that the associated pharmaceutical compositions are useful for treating a subject suffering from, or predisposed to a disease or disorder.

Dose Regimens

In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising about 0.2 mg to about 16 mg of the anti-TSLP antigen binding fragment. For example, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising about 0.2 mg, about 0.4 mg, about 0.6 mg, about 2 mg, about 6 mg, about 8 mg or about 16 mg of the anti-TSLP antigen binding fragment. In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising about 0.4 mg to about 8 mg of the anti-TSLP antigen binding fragment. For example, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a

dose comprising about 0.4 mg, about 2 mg, or about 8 mg of the anti-TSLP antigen binding fragment. In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising about 0.5 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, or about 16 mg of the anti-TSLP antigen binding fragment.

In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising 0.2 mg to 16 mg of the anti-TSLP antigen binding fragment. For example, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising 0.2 mg, 0.4 mg, 0.6 mg, 2 mg, 6 mg, 8 mg or 16 mg of the anti-TSLP antigen binding fragment. In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising 0.4 mg to 8 mg of the anti-TSLP antigen binding fragment. For example, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising 0.4 mg, 2 mg, or 8 mg of the anti-TSLP antigen binding fragment. In some instances, the pharmaceutical composition is administered or is to be administered to a subject in need thereof at a dose comprising 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, or 16 mg of the anti-TSLP antigen binding fragment.

In some instances, the dose of the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof once per day. In some instances, the dose of the anti-TSLP antigen binding fragment administered to or to be administered to the subject in need thereof is a daily dose. In some instance, the dose of the anti-TSLP antigen binding fragment administered to or to be administered to the subject in need thereof is the total daily dose. In some instances, the dose of the TSLP antigen binding fragment is administered or is to be administered to the subject in need thereof every other day. In some instances, the dose of the anti-TSLP fragment is administered or is to be administered to the subject in need thereof daily. In some instances, the dose of the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof twice a day or once a day. In some instances, the dose of the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof once daily (Q1D).

In some instances, the pharmaceutical composition comprising the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof for at least 2 weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least seven months, at least eight months, at least nine months, at least ten months, at least eleven months, or at least twelve months. In some instances, the pharmaceutical composition comprising the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof for at least 2 weeks, at least 4 weeks, at least 8 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks, at least 28 weeks, at least 32 weeks, at least 36 weeks, at least 40 weeks, at least 44 weeks, at least 48 weeks, or at least 52 weeks. In some instances, the pharmaceutical composition comprising the anti-TSLP antigen binding fragment is administered or is to be administered to a subject in need thereof for about 12 to about 52 weeks, e.g. for 12 to 52 weeks.

In some instances, the pharmaceutical composition comprising the anti-TSLP antigen binding fragment is administered or is to be administered to the subject orally or intranasally, e.g. in aerosolized form. In some instances, the pharmaceutical composition comprising the antigen binding fragment is administered or is to be administered to the subject by inhalation, e.g. by using a dry powder inhaler. In some instances, the pharmaceutical composition comprising the antigen binding fragment is administered or is to be administered to the subject by oral inhalation, e.g. by using a dry powder inhaler.

The dose of the anti-TSLP antigen binding fragment to be administered to or administered to the patient is the target amount of the anti-TSLP antigen binding fragment present in the pharmaceutical composition, e.g. a dry powder formulation, for administration to the patient. For example, it may be the dose present in an inhalation device for administration the patient, e.g. the dose may be the nominal metered dose for addition to an inhalation device, such as a dry powder inhaler. In some instances, the dose may be the amount of the anti-TSLP antigen binding fragment present in a capsule comprising the pharmaceutical composition, e.g. as a dry powder formulation, for addition to an inhalation device, e.g. a dry powder inhaler.

The features disclosed in the foregoing description, or in the following claims, or in the accompanying drawings, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or process for obtaining the disclosed results, as appropriate, may, separately, or in any combination of such features, be utilised for realising the disclosure in diverse forms thereof.

While the disclosure has been described in conjunction with the exemplary instances described above, many equivalent modifications and variations will be apparent to those skilled in the art when given this disclosure. Accordingly, the exemplary instances of the disclosure set forth above are considered to be illustrative and not limiting. Various changes to the described instances may be made without departing from the spirit and scope of the disclosure.

For the avoidance of any doubt, any theoretical explanations provided herein are provided for the purposes of improving the understanding of a reader. The inventors do not wish to be bound by any of these theoretical explanations.

Any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise" and "include", and variations such as "comprises", "comprising", and "including" will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range

is expressed, another instance includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another instance. The term "about" in relation to a numerical value is optional and means for example $\pm 20\%$. When the term " $\pm x\%$ " is used herein, it refers to a percentage of the value preceding it, rather than adding or subtracting the absolute percentage listed, e.g. "20% $\pm 10\%$ " means "18-22%", rather than "10-30%".

Examples

These examples demonstrate the optimisation of buffer conditions, components, and pH (Example 2), histidine strength and leucine/trileucine levels (Examples 3-4) to arrive at a stable FAB1 powder formulation (Example 5) that shows minimal *in vitro* aggregation and a favourable toxicology profile (Example 6).

EXAMPLE 1 - Background

FAB1 is an antibody fragment directed against the cytokine TSLP and may be used for treatment of moderate to severe asthma patients. The route of administration is inhalation of a dry powder formulation via a dry powder inhaler (DPI). The selected phase 1 formulation comprised trehalose, leucine, trileucine and citrate (TLTC) at pH 6 with addition of polysorbate 80 (PS80) to mitigate protein aggregations and keep low counts of subvisible particles. However, the surfactant resulted in impaired powder properties mainly by reduced manufacturing yield and significant elevation of the powder retention in device and throat. Therefore, alternative formulations for FAB1 were developed, and the formulation of different buffers (citrate vs histidine (trehalose, leucine, trileucine and histidine (TLTH)), pH, histidine strength, and leucine/trileucine levels were tested to arrive at an optimal formulation.

Three screening studies and a stability study were performed:

- Study 1: TLTC vs TLTH at pH 5 and 6
- Study 2: TLTH at 1.3% Histidine, addition of PS80, different levels of trileucine and leucine (e.g. 2x trileucine/leucine and high leucine no trileucine).
- Study 3: TLTH titration of optimal histidine levels
- Study 4: Stability (1M accelerated) TLTH

Selection criteria for drug product were based on aerosol performance, solid state characterisation, and protein aggregate formation upon reconstitution of dry powder.

EXAMPLE 2 – Study 1: TLTC vs TLTH at pH 5 and 6

Experimental

This study evaluated two factors of the formulation, namely buffer (citrate vs histidine) and pH (5 and 6).

To test the effect of histidine buffer at different pH on protein formulation and protein aggregation, six batches were produced as shown in **Table 5**. The composition of each batch is summarised in **Table 6**.

Lot number	Formulation	FAB1 Strength	Batch size (g)	FS Vol (ml)
21-WS-016	TLTC, pH 5	10%	10	133
21-WS-017	TLTC, pH 5	40%		
21-WS-018	TLTH, pH 6, 5% His	10%		
21-WS-019	TLTH, pH 6, 5% His	40%		
21-WS-023	TLTH, pH 5, 5% His	10%		
21-WS-024	TLTH, pH 5, 5% His	40%	20	267

Table 5. Study 1 Batches

Component (% w/w)	10% FAB1, TLTC, pH 5	40% FAB1, TLTC, pH 5	10% FAB1, TLTH, pH 6	40% FAB1, TLTH, pH 6	10% FAB1, TLTH, pH 5	40% FAB1, TLTH, pH 5
Lot	21-WS-016	21-WS-017	21-WS-018	21-WS-019	21-WS-023	21-WS-024
FAB1	10.0	40.0	10.0	40.0	10.0	40.0
Trehalose	69.55	39.55	72.70	42.70	72.05	42.05
Leucine	10.50	10.50	10.50	10.50	10.50	10.50
Trileucine	2.00	2.00	2.00	2.00	2.00	2.00
Trisodium citrate	5.50	5.50	-	-	-	-
Citric acid	2.45	2.45	-	-	-	-
L-Histidine	-	-	2.00	2.00	0.35	0.35
Histidine- HCl	-	-	2.80	2.80	5.10	5.10

Table 6. Study 1 Formulation Targets

Results

Description		10% TLTC, pH 5 (21- WS-016)	40% TLTC, pH 5 (21- WS-017)	10% TLTH, pH 6 (21- WS-018)	40% TLTH, pH 6 (21- WS-019)	10% TLTH, pH 5 (21- WS-023)	40% TLTH, pH 5 (21- WS-024)
Formulation	Batch size (g)	10	10	10	10	10	20
	Solids loading (mg/ml)	75	75	75	75	75	75
	Feedstock (FS) Volume (ml)	133.3	133.3	133.3	133.3	133.3	166.6
Yield (based on batch size) (%)		69.6	87.4	69.3	67.7	79	68.6
Yield (based on FS mass) (%)		75.0	94.2	81.5	79.6	85.3	71.1

FS pH	5.1	5.1	6.0	5.8	5.0	5.1
-------	-----	-----	-----	-----	-----	-----

Table 7. Study 1 processing results. 1) Yield based on batch size is calculated as the net collector yield divided by the nominal batch size. 2) Yield based on FS mass is calculated as the net collector yield divided by the actual FS mass.

Table 6 shows that all batches were at 10g batch size except for the 40% TLTH, pH 5, which was 20g.

- 5 Despite the small batch sizes, the spray drying yield based on FS mass was high for all of them. The powders were produced at low throughput processing parameters.

		10% FAB1			40% FAB1		
		TLTC pH5 (21- WS-016)	TLTH pH6 (21- WS-018)	TLTH pH5 (21- WS-023)	TLTC pH5 (21- WS-017)	TLTH pH6 (21- WS-019)	TLTH pH5 (21- WS-024)
Drug Substance (DS) protein	mg/ml	42.8	44.7	41.7	42.8	44.7	41.8
	% recovery	85	85	84	85	85	84
FS protein	mg/ml	7.1	7.0	7.3	28.9	27.5	29.0
	% recovery	94	94	97	97	92	97
Bulk powder (BP) protein	% w/w	9.4	9.7	7.6*	35.5	37.0	36.4
	% recovery	93.9	96.6	75.7	88.8	92.6	91.0
DS High performance size exclusion chromatography (HP-SEC)	% monomer primary peak (MPP)	99.9	100	99.8	99.9	100	99.8
	% aggregates	0.1	0.0	0.2	0.1	0.0	0.20
FS HP-SEC	% MPP	99.9	99.9	99.8	99.9	99.9	99.8
	% aggregates	0.1	0.1	0.2	0.1	0.1	0.2
BP HP-SEC	% MPP	99.9	99.9	99.7	99.9	99.9	99.7
	% aggregates	0.1	0.1	0.3	0.1	0.1	0.3
Primary particle size distribution (pPSD)	d10 (µm)	0.5	0.5	0.5	0.5	0.5	0.5
	d50 (µm)	1.5	1.5	1.8	1.7	1.8	1.5
	d90 (µm)	3.5	3.5	3.8	3.8	3.9	3.4
	Span	2.0	2.0	1.9	1.9	1.9	2.0

Moisture content (%)	1.4	0.7	0.7	1.5	1.0	0.9
Glass transition temperature (T _g) (°C)	94	98	99	97	100	99
Compressed Bulk Density (cBD) (g/cm ³)	0.6584	0.7245	0.7498	0.6070	0.6479	0.6702
Specific Surface Area (SSA) (m ² /g)	5.8251	5.1879	4.9904	5.5543	5.5313	5.2441

Table 8. Study 1 solid state testing. *Lower value than expected and does not align with the FS protein concentration (97% recovery)

Table 8 shows that the solid properties were similar between all formulations and that protein purity was very high in DS, FS and BP with low aggregation. Primary particle size distribution was similar across all formulations and moisture content was low, being below 1% for the histidine formulations. Glass transition was high and similar for all formulations. High glass transition and low residual moisture content suggest room temperature stable powder. Compressed bulk density was in a favourable range with slightly higher numbers for the TLTH formulations indicating a slightly more flowable powder also reflected in a slightly increased surface area.

Scanning Electron Microscopy (SEM) analysis of the formulations demonstrated good morphology with similar appearance for both the TLTC and TLTH formulations (**Figure 1**).

A critical readout for the dry powder formulation is the protein aggregation following reconstitution. Using Mass Flow Imaging (MFI), the number of particles were counted in powder reconstituted to two concentrations, 2.5 mg/ml protein and the feedstock concentration of 30mg/ml.

Figure 2 shows the number of particles present in the tested powder formulations (TLTC pH 5 (21-WS-016); TLTH pH 6 (21-WS-018); and TLTH pH 5 (21-WS-023)). Particle counts were significantly higher with the TLTC formulation compared with TLTH, having “low” particle counts at 2.5mg/ml and at feedstock concentration.

Figure 3 shows the number of particles in the tested powder formulations (TLTC pH 5 (21-WS-017); TLTH pH 6 (21-WS-019); and TLTH pH 5 (21-WS-024)). Particle counts were higher with the TLTC formulation compared to TLTH at feedstock concentration but not at 2.5 mg/ml.

Figure 4 shows the number of particles in the tested formulations (Drug substance citrate pH 5; Drug substance histidine pH 6; Drug substance histidine pH 5). Notably, DS in TLTC had higher particle counts than DS in TLTH where pH 5 was lower than pH 6. The same trend was observed for FS (Figures 4B and C).

Figure 5 compares reconstituted powder with 10% and 40% FAB1 across the different formulations, and the lowest particle counts were observed for TLTH, pH 5 (see Figure 5C).

Together, **Figures 2 to 5** show that particle counts in DS, FS and reconstituted BP all followed the same pattern with lowest counts in TLTH, pH 5, slightly higher in TLTH, pH 6, and significantly higher in TLTC, pH 5. Due to the significantly higher levels of protein aggregation in the citrate-containing buffers, the histidine buffer was considered superior.

- 5 Finally, aerosol performance of the 10% and 40% lots was tested using a cascade impactor for pharmaceutical inhaler testing (see **Figures 6 and 7**). The deposition profiles for FAB1 were collected using a flow rate of 30.0 ± 1.0 L/min and a Next Generation Impactor, as described by United States Pharmacopeia (USP) <601> Apparatus 6. The Next Generation Impactor consists of seven stages, or sample receptacles, that are rated at different mass median aerodynamic diameter values which depend
- 10 on the flow rate, the NGI is also fitted with an USP induction port, "throat", to accommodate the inhaler device. The inhaler device is "actuated" when a vacuum pump imposes a given flow rate, simulating a patient inspiration through the device's mouthpiece. Active agent amounts left in the device, including capsule, as well on throat, and on each of the stages is determined with an appropriate analytical method after each actuation. Aerosol performance is comparable across the formulations, with a very high
- 15 (>80%) fine particle fraction (FPF) (<5 μ m) and favourable median mass aerodynamic diameter (MMAD) of 2.5 microns (± 0.5). The device deposition was low for all formulations, and lowest for the TLTH formulations.

The above results indicate that the histidine buffer is superior to the citrate buffer in terms of keeping the protein aggregation low.

20 EXAMPLE 3 – Study 2: TLTH with PS80 and Trileucine/Leucine

Experimental

- Study 2 was designed to explore the formulation space for histidine and the shell-forming excipients leucine and trileucine. The first goal was to study the effect of reduced histidine on the particle surface by decreasing the total amount of histidine in the formulation (from 5% to 1.3%) or by increasing the
- 25 leucine/trileucine ratio. Addition of a small amount of PS80 was also explored.

- A design of experiments (DOE) was established to explore the design space for the formulation components focusing on subvisible particle counts and aerosol performance and device deposition as critical read out parameters. Factors for evaluation were 1) reduction in histidine, 2) increase shell-
- 30 forming excipients to decrease the amount of histidine on the surface, 3) addition of optimized amount of PS80. Addition of PS80 results in increased device deposition, although it significantly reduces the protein aggregation and keeps the particle counts low (see WO2021/083908). Increasing the shell forming components trileucine and leucine was explored to improve the moisture robustness of the powder. Finally, a formulation with very high leucine (37.5%) and no trileucine was added to study
- 35 moisture robustness. Nine batches were produced as shown in **Table 9**. The composition of each batch is summarised in **Table 10**.

Lot number	Formulation	FAB1 Strength	Batch size (g)	FS Vol. (ml)
21-WS-039	TLTH, pH 5.5, 1.3 % His	10%	15	200
21-WS-040	TLTH, pH 5.5, 1.3 % His	40%		
21-WS-041	TLTH, pH 5.5, 1.3 % His, 2x TriLeu/Leu	10%		
21-WS-042	TLTH, pH 5.5, 5 % His, 2x TriLeu/Leu	10%		
21-WS-043	TLTH, pH 5.5, 1.3 % His, 0.4% PS80	10%		
21-WS-044	TLTH, pH 5.5, 1.3 % His, 0.4% PS80	40%		
21-WS-045	TLTH, pH 5.5, 5 % His	10%		
21-WS-046	TLTH, pH 5.5, 5 % His	40%		
21-WS-060	TLH, pH 5.5, 1.3% His, 37.5% Leu	10%		

Table 9. Study 2 batches

Component (% w/w)	10% FAB1 1.3% His	40% FAB1 1.3% His	10% FAB1 1.3% His 2x Leu/trileu	10% FAB1 5% His 2x 3Leu/Leu, 0.4% PS80	10% FAB1 1.3% His 0.4% PS80	40% FAB1 1.3% His 0.4% PS80	10% FAB1 5% His	40% FAB1 5% His	10% FAB1 1.3% His 37.5% Leu
Lot	21-WS-039	21-WS-040	21-WS-041	21-WS-042	21-WS-043	21-WS-044	21-WS-045	21-WS-046	21-WS-060
FAB1	10.0	40.0	10.0	10.0	10.0	40.0	10.0	40.0	10.0
Trehalose	76.17	46.17	63.67	59.69	75.77	45.77	72.59	42.59	53
Leucine	10.50	10.50	21.0	21.0	10.5	10.5	10.5	10.5	37.5
Trileucine	2.0	2.0	4.0	4.0	2.0	2.0	2.0	2.0	-
PS80	-	-	-	0.4	0.4	0.4	-	-	-
L-Histidine	0.25	0.25	0.25	0.93	0.25	0.25	0.93	0.93	0.23
Histidine-HCl	1.08	1.08	1.08	3.98	1.08	1.08	3.98	3.98	1.07

Table 10. Study 2 formulation targets

Results

Table 11 is summary of the study processing results, including actual processing parameters and yields.

Lot		21-WS-039	21-WS-040	21-WS-041	21-WS-042	21-WS-043	21-WS-044	21-WS-045	21-WS-046	21-WS-060
Description		10% TLTH 1.3% His	40% TLTH 1.3% His	10% TLTH 1.3% His 2x Leu/Trileu	10% TLTH 5% His 2x Leu/trileu, 0.4% PS80	10% TLTH 1.3% His 0.4% PS80	40% TLTH 1.3% His 0.4% PS80	10% TLTH 5% His	40% TLTH 5% His	10% TLTH 1.3% His 37.5% Leu
Form	Batch size (g)	15	15	15	15	15	15	15	15	15
	Solids loading (mg/ml)	75	75	75	75	75	75	75	75	75
	Feedstock (FS) Volume (ml)	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00	200.00
Yield (based on batch size) (%)		80.7	70.7	63.3	60.1	87.0	82.3	87.6	83.2	84.6
Yield (based on FS mass) (%)		85.0	74.5	84.8	80.1	92.9	87.9	81.6	77.3	87.8
FS density (g/ml)		1.0238	1.0213	1.0214	1.0207					
FS pH		5.3	5.5	5.5	5.5	5.4	5.4	5.4	5.3	5.4

Table 11. Study 2 processing results. 1) Yield based on batch size is calculated as the net collector yield divided by the nominal batch size. 2) Yield based on FS mass is calculated as the net collector yield divided by the actual FS mass.

		10% FAB1						40% FAB1		
		TLTH 1.3% His (21-WS-039)	TLTH 1.3% His 2x Leu/trileu (21-WS-041)	TLTH 5% His 2x 3Leu/Leu, 0.4% PS80 (21-WS-42)	TLTH 1.3% His 0.4% PS80 (21-WS-043)	TLTH 5% His (21-WS-045)	TLTH 1.3% His 37.5% Leu (21-WS-60)	TLTH 1.3% His (21-WS-40)	TLTH 1.3% His 0.4% PS80 (21-WS-044)	TLTH 5% His (21-WS-046)
Drug Substance (DS) protein	mg/ml	54.0	53.0	53.0	53.9	52.8	59.1	54.0	53.0	52.8
	% recovery	98	96	96	98	96	98	98	96	96
FS protein	mg/ml	7.4	7.5	7.6	7.6	7.6	4.9	30.0	29.8	30.1

	% recovery	99	100	102	101	101	98.8	100	99	100
Bulk powder (BP) protein	% w/w	9.9	10.2	10.2	9.8	10.0	9.7	38.8	39.8	39.3
	% recovery	99.5	101.6	101.6	98.3	99.6	97.4	97	99.4	98.3
DS High performance size exclusion chromatography (HP-SEC)	% MPP	100	100	100	100	100	100	100	100	100
	% aggregates	0	0	0	0	0	0	0	0	0
FS HP-SEC	% MPP	100	100	100	100	100	99.4	100	100	100
	% aggregates	0	0	0	0	0	0.6	0	0	0
BP HP-SEC	% MPP	100.0	99.9	99.9	100.0	100.0	99.6	99.9	99.9	99.9
	% aggregates	0.0	0.1	0.1	0.0	0.0	0.4	0.1	0.1	0.1
Primary particle size distribution (pPSD)	d10 (µm)	0.5	0.5	0.5	0.5	0.5	0.5/0.4 ¹	0.5	0.5	0.5
	d50 (µm)	1.5	1.6	1.7	1.5	1.6	1.7/1.3 ¹	1.7	1.7	1.7
	d90 (µm)	3.5	3.6	3.6	3.5	3.6	4.5/3.1 ¹	3.9	3.9	3.9
	Span	2.0	1.9	1.9	2.0	1.9	2.4/2.0 ¹	2.0	1.9	2.0
Moisture content (%)		0.9	0.9	0.7	0.7	0.6	0.6	1.0	0.9	1.1
Glass transition temperature (Tg) (°C)		100	100	98	102	100	108	104	81, 104 ²	100
Compressed Bulk Density (cBD) (g/cm ³)		-	-	-	-	-	0.6969	-	-	-
Specific Surface Area (SSA) (m ² /g)		-	-	-	-	-	5.4687	-	-	-

Table 12. Study 2 solid state testing. ¹Larger particle size than expected on initial testing, so pPSD test repeated. ²Values refer to Tg onset and 2nd Tg onset.

Scanning Electron Microscopy (SEM) analysis of the formulations demonstrated good morphology with similar appearance for both the TLTC and TLTH formulations (**Figures 8 and 9**).

- 5 MFI results for the 10% FAB1 are shown in **Figure 10**. All formulations showed low particle counts compared with the TLTC formulation (21-WS-016 – see Figure 5). Addition of PS80 further reduced the particle counts (21-WS-042 and 043). Doubling leucine and trileucine had no impact on the particle counts.

- 10 MFI results for the 40% FAB1 are shown in **Figure 11**. All formulations showed low particle counts compared with the TLTC formulation (21-WS-017). Addition of PS80 further reduced the particle counts (21-WS-044). There is a trend towards lower particle counts with 1.3% histidine compared with 5% histidine. Similar results for pH 5, pH 5.5 and pH 6.

Finally, aerosol performance of the 10% and 40% lots was tested using a cascade impactor for pharmaceutical inhaler testing (see **Figures 12 and 13**).

When comparing TLTH formulations with 5% histidine and pH at 5, 5.5 or 6, no significant differences were observed for solid state properties (**Table 12**), aerosol performance and protein aggregation (**Figures 12 and 13**). In the DOE analysis and modelling of histidine vs PS80 it was concluded that higher histidine and lower PS80 levels were beneficial to lower device deposition, while only PS80 affected the protein aggregations. Addition of high leucine/trileucine also had no significant impact on the device deposition or protein aggregation. Moisture content and glass transition temperature were similar for all formulations. PS80 at a low level (0.4%) showed tendency of stickiness with lower spray drying yield and higher device deposition (**Figures 12 and 13**) but kept, as expected, the protein aggregations to a minimal (**Table 12**).

10 Conclusion

Together these data show that higher concentrations of histidine combined with lower levels of PS80 reduces device deposition. The formulation containing TLTH at pH 5.5 keeping trileucine at 2.0% w/w and leucine at 10.5% w/w with no addition of PS80 showed favourable properties. Therefore, the inventors further optimised this formulation by investigating the optimal histidine concentration.

15 EXAMPLE 4 – Study 3: TLTH optimal histidine levels

Experimental

Study 3 investigates the optimum histidine concentration for the TLTH formulation. Three levels of histidine were explored to select the optimal concentration. Six batches were produced as shown in **Table 13**. The composition of each batch is summarized in **Table 14**.

Lot number	Formulation	FAB1 Strength	Batch size (g)	FS Vol. (ml)
21-WS-055	TLTH, pH 5.5, 1.3 % His	10%	15	200
21-WS-056	TLTH, pH 5.5, 3.14 % His	10%		
21-WS-057	TLTH, pH 5.5, 5 % His	10%		
21-WS-058	TLTH, pH 5.5, 3.14 % His	40%		
21-WS-059	TLTH, pH 5.5, 5 % His	40%		
21-WS-061	TLTH, pH 5.5, 1.3 % His	40%		
21-WS-045	TLTH, pH 5.5, 5 % His	10%		
21-WS-046	TLTH, pH 5.5, 5 % His	40%		
21-WS-060	TLH, pH 5.5, 1.3% His, 37.5% Leu	10%		

20 **Table 13. Study 3 batches**

Component (% w/w)	10% FAB1 1.3% His	10% FAB1 3.14% His	10% FAB1 5% His	40% FAB1 3.14% His	40% FAB1 5% His	40% FAB1 1.3% His
Lot	21-WS-055	21-WS-056	21-WS-057	21-WS-058	21-WS-059	21-WS-061
FAB1	10.0	10.0	10.0	40.0	40.0	40.0
Trehalose	76.20	74.36	72.52	44.36	42.52	46.16
Leucine	10.50	10.50	10.50	10.50	10.50	10.50
Trileucine	2.00	2.00	2.00	2.00	2.00	2.00
L-Histidine	0.23	0.55	0.88	0.55	0.88	0.37
Histidine- HCl	1.07	2.59	4.10	2.59	4.10	0.97

Table 14. Study 3 formulation targets

Results

Table 15 shows a summary of the study 3 processing results, including actual processing parameters and yields. Solid state testing results are shown in **Table 16** and SEM images are shown in **Figure 14**.

5

Lot		21-WS-055	21-WS-056	21-WS-057	21-WS-058	21-WS-059	21-WS-061
Description		10% TLTH, 1.3% His	10% TLTH, 3.14% His	10% TLTH, 5% His	40% TLTH, 3.14% His	40% TLTH, 5% His	40% TLTH, 1.3% His
Formulation	Batch size (g)	15	15	15	15	15	15
	Solids loading (mg/ml)	75	75	75	75	75	75
	Feedstock (FS) Volume (ml)	200.00	200.00	200.00	200.00	200.00	200.00
Yield (based on batch size) (%)		79.9	85.2	81.8	74.3	66.7	85.2
Yield (based on FS mass) (%)		83.4	88.9	85.4	77.4	69.6	89.2
FS pH		5.4	5.4	5.5	5.4	5.4	5.7

Table 15. Study processing results

		10% FAB1			40% FAB1		
		TLTH 1.3% His (21-WS-055)	TLTH 3.14% His (21-WS-056)	TLTH 5% His (21-WS-057)	TLTH 1.3% His (21-WS-061)	TLTH 3.14% His (21-WS-058)	TLTH 5% His (21-WS-059)
Drug Substance (DS) protein	mg/ml	59.1	59.1	59.1	52.4	59.1	59.1
	% recovery	98	98	98	96	98	98
FS protein	mg/ml	7.4	7.4	7.4	28.6	29.5	29.4
	% recovery	99.1	98.4	98.9	95.5	98.1	98.1
Bulk powder (BP) protein	% w/w	10.2	10.3	10.3	37.9	41.0	40.8
	% recovery	102.3	103.4	102.6	94.8	102.6	102.1
DS High performance size exclusion chromatography (HP-SEC)	% MPP	100	100	100	100	100	100
	% aggregates	0	0	0	0	0	0
FS HP-SEC	% MPP	100	100	100	100	100	100
	% aggregates	0	0	0	0	0	0
BP HP-SEC	% MPP	100.0	100.0	100.0	99.9	99.9	99.9
	% aggregates	0.0	0.0	0.0	0.1	0.1	0.1
Primary particle size distribution (pPSD)	d10 (µm)	0.5	0.5	0.5	0.6 / 0.4	0.5	0.5
	d50 (µm)	1.6	1.6	1.6	2.1 / 1.7	1.7	1.6
	d90 (µm)	3.6	3.6	3.7	5.0 / 3.9	4.1	3.9
	Span	2.0	2.0	2.0	2.2 / 2.0	2.1	2.1
Moisture content (%)		0.7	0.7	0.7	0.9	1.0	1.0
Glass transition temperature (Tg) (°C)		101, 103	100, 102	100, 101	116	99, 105	100, 102
Compressed Bulk Density (cBD) (g/cm³)		0.6131	0.6901	0.6558	0.5529	0.6226	0.5378
Specific Surface Area (SSA) (m²/g)		4.8447	5.2046	4.9938	5.7128	5.7473	5.8758

Table 16. Study 3 solid state testing

All TLTH formulations show excellent solid-state properties based on the following criteria: D90<5µm (90% of the particles less than 5µm), %water <5%, Tg >80°C at 2% water content.

Subvisible particles detected by MFI were low for all TLTH formulations (see **Figures 15 and 16**).

- 5 The NGI results for the 10% and 40% are plotted in **Figures 17A and B** and summarised in **Figure 17**, and these data indicate that aerosol performance is very good at all histidine concentrations.

Conclusions

- Three levels of histidine 1.3%, 3.14% and 5% were explored at 10% and 40% protein strength to establish optimal histidine concentration. There was no significant difference in solid-state or aerosol
10 performance between the different formulations and protein aggregations were low with a small trend for lower numbers at the higher histidine levels.

EXAMPLE 5 – Study 4: 1 month stability of TLTH

Experimental

- Study 4 was added to gain insight in the stability of the TLTH formulation with optimized histidine and pH.
15 Powder and filled capsules previously manufactured in studies 1-3 were used for the stability testing, as shown in **Table 17**. High (5%) and low (1.3%) histidine formulations were set down at 40°C/75% RH (protected with foil overwrap and desiccant) to support TLTH as the proposed phase 2 formulation. NLT 2g of powder for each lot was transferred into aluminum Tournaire containers and foil overwrapped with desiccant and a stability test was performed for 1 month at 40°C/75%RH. Capsules were filled and
20 packed in foil pouches with desiccant and stored protected at 40°C/75%RH.

Lot number	Formulation	FAB1 Strength
21-WS-039	TLTH, pH 5.5, 1.3 % His	10%
21-WS-040	TLTH, pH 5.5, 1.3 % His	40%
21-WS-045	TLTH, pH 5.5, 5 % His	10%
21-WS-046	TLTH, pH 5.5, 5 % His	40%
21-WS-056	TLTH, pH 5.5, 3.14 % His	10%
21-WS-058	TLTH, pH 5.5, 3.14 % His	40%

Table 17. Study 4 Stability batches

Results

Tables 18 and 19 summarise the solid-state stability results, and SEM images are shown in **Figure 18**.

Formulation		TLTH 1.3% His		TLTH 3.14% His		TLTH 5% His	
Lot number		21-WS-039		21-WS-056		21-WS-045	
Time point (months)		T=0	T=1	T=0	T=1	T=0	T=1
BP protein	% w/w	9.9	9.43	10.3	9.81	10	9.59
	% Recovery	99.5	94.3	103.6	98.1	99.6	95.9
BP HP-SEC	% MPP	100	100	100	100	100	99.9
	% Aggregates	0.0	0.0	0.0	0.0	0.0	0.1
pPSD	d10 (µm)	0.5	0.4	0.5	0.5	0.5	0.4
	d50 (µm)	1.5	1.5	1.6	1.6	1.6	1.6
	d90 (µm)	3.5	3.5	3.6	3.6	3.6	3.6
	Span	2.0	2.1	2.0	2.0	1.9	2.0
Moisture content (%)		0.9	1.2, 1.6*	0.7	0.7	0.6	1, 1.3*

Table 18. Stability results 10% FAB1 TLTH formulation. *KF was rerun to confirm a slight increase in moisture content in two of the formulations.

Formulation		TLTH 1.3% His		TLTH 3.14% His		TLTH 5% His	
Lot number		21-WS-040		21-WS-058		21-WS-046	
Time point (months)		T=0	T=1	T=0	T=1	T=0	T=1
BP protein	% w/w	38.3	36.4	41.0	39.3	39.3	37.8
	% Recovery	97.0	88.1, 91.0*	103	98.4	98.3	90.1, 94.4*
BP HP-SEC	% MPP	99.9	99.9	99.9	99.9	99.9	99.9
	% Aggregates	0.1	0.1	0.1	0.1	0.1	0.1
pPSD	d10 (µm)	0.5	0.4	0.5	0.5	0.5	0.4
	d50 (µm)	1.7	1.7	1.7	1.6	1.7	1.7
	d90 (µm)	3.9	3.9	4.1	3.7	3.9	3.9
	Span	2.0	2.1	2.1	2.0	2.0	2.1
Moisture content (%)		1.0	1.1, 1.2*	1.0	1.0	1.1	1.2, 1.3*

Table 19. Stability results 40% FAB1 TLTH formulation. *KF was rerun to confirm a slight increase in moisture content in two of the formulations.

- 5 The NGI results for Study 4 are shown in **Figures 19** and **20** and summarised in **Tables 20** and **21**.

Formulation	TLTH 1.3% His		TLTH 3.14% His		TLTH 5% His	
Lot number	21-WS-039		21-WS-056		21-WS-045	
Time point (months)	T=0	T=1	T=0	T=1	T=0	T=1
FPF (<5µm) (%)	78	83	78	81	84	78
FPM (<5µm) (mg)	1.4	1.6	1.4	1.5	1.6	1.5
MMAD (µm)	2.7	2.6	2.7	2.7	2.7	2.9

Table 20. NGI 1 Month Accelerated Stability Results 10% FAB1.

Formulation	TLTH 1.3% His		TLTH 3.14% His		TLTH 5% His	
Lot number	21-WS-040		21-WS-058		21-WS-046	
Time point (months)	T=0	T=1	T=0	T=1	T=0	T=1
FPF (<5µm) (%)	82	80	81	85	81	80
FPM (<5µm) (mg)	5.8	5.6	6.1	6.3	5.8	5.5
MMAD (µm)	2.8	2.6	2.5	2.6	2.6	2.8

Table 21. NGI 1 Month Accelerated Stability Results 40% FAB1.

Conclusions

All formulations performed very well, and the formulation containing TLTH, pH 5.5 with 3.14% histidine (w/w) showed especially good stability.

EXAMPLE 6 – *in vivo* toxicity study

To test the *in vivo* toxicity of inhaled FAB1 Fab in powder formulation using the new formulation as described in Example 5 (TLTH, pH 5.5 with 3.14% histidine (w/w)), a 28-day good laboratory practice (GLP) toxicity study was set up and compared with an earlier toxicity study using TLTC, pH 6 with PS80.

Group	Dose	Exposure Duration (Minutes)	Total Aerosol Dose Level (mg/L)	FAB1 Aerosol Dose Level (mg/L)	Deposited Dose Level (mg/kg/d)	Animals	
						Main Study	Recovery
1	Air Control	60	LLOQ	LLOQ	0	3M + 3F	2M + 2F
2	Placebo Control	60	2.5	LLOQ	0	3M + 3F	
3	Low Dose	8	2.5	963	1.0	3M + 3F	
4	Mid Dose	20	2.5	958	2.3	3M + 3F	2M + 2F
5	High Dose	60	2.5	893	7.1	3M + 3F	2M + 2F

Table 22. 28-Day Cyno GLP toxicity study results with FAB1 in TLTC, pH 6 with PS80. LLOQ = lower limit of quantification.

Table 22 shows the study results of a first 28-day toxicity study in which cynomolgus monkeys were treated with FAB1 reconstituted in TLTC at pH 6 with PS80. No adverse effects were seen on food consumption, body weights, clinical observations, clinical pathology, pulmonary function tests, ECGs, blood pressure, neurobehavioral assessments, or ophthalmology.

There were also no adverse macroscopic or microscopic findings for all tissues including respiratory tract (*i.e.* lungs, trachea, larynx, oesophagus, salivary glands, lymph nodes, tongue, tonsils, soft palate) for animals treated with low dose levels (deposited dose level of 1.0 mg/kg/day).

However, at the higher doses of 2.3 (females only) and 7.1 mg/kg/day (both sexes) an increase of FAB1-related incidence and/or severity of lung perivascular (PV)/peribronchiolar (PB) mononuclear inflammatory cell (MIC) infiltrates (see **Figure 21**). The no-observed-adverse-effect-level (NOAEL) was therefore 1 mg/kg/day in this first study using TLTC at pH 6 + PS80 as excipient.

Figure 22 further shows visible particles in the reconstituted formulation (FAB1 in TLTC at pH 6 with PS80) in water, which is a simplistic simulation of the expected reconstitution in epithelial lining fluid after lung deposition.

Group	Dose	Exposure Duration (Minutes)	Total Aerosol Dose Level (mg/L)	FAB1 Aerosol Conc Level (mg/L)	Target Delivered Dose Level (mg/kg/d)	Target Lung Deposited Dose Level (mg/kg/d)	Animals
							Main Study
1	Air Control	60	0	0	0	0	3M + 3F
2	Placebo Control	60	0.724	LLOQ	0	0	3M + 3F
3	Low Dose	60	NC (0.090)	36	1.2	0.3	3M + 3F
4	Mid Dose	60	NC (0.303)	121	4	1	3M + 3F
5	High Dose	60	0.72	278	9.2	2.3	3M + 3F

Table 23. 28-Day Cyno GLP toxicity study results with FAB1 in TLTH, pH 5.5 with 3.14% histidine. LLOQ = lower limit of quantification.

Table 23 shows the results of a second 28-day toxicity study in which cynomolgus monkeys were treated with TLTH, pH 5.5 with 3.14% histidine (w/w).

- 5 **Figure 23** shows representative images of FAB1-related lung pathology. Mononuclear cell (MNC) infiltrates in the lungs were minimal, for all tested doses. Microscopic findings were suggestive of a localised low-grade immune response to an inhaled foreign protein and were considered non-adverse (**Figure 24**). The NOAEL in this study was 2.3 mg/kg deposited dose (as opposed to 1 mg/kg deposited dose for the first toxicity study).
- 10 Taken together, the above data show that the common microscopic finding associated with inhaled proteins in cynomolgus monkeys is mononuclear inflammatory cell (MIC) infiltrate in the lung. In the first 28-day toxicity study, PB/PB MIC infiltrates were observed, at a severity that was considered adverse and limited the NOAEL to 1 mg/kg. A TLTH formulation with pH 5.5 and 3.14% histidine (w/w) was associated with decreased *in vitro* aggregation and exhibited a more favorable toxicology profile (2.3 mg/kg NOAEL
- 15 vs 1mg/kg NOAEL) in cynomolgus monkeys compared with TLTC, pH 6 with PS80.

EXAMPLE 7 – Phase I, Randomised, Blinded, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of FAB1 in Healthy Adult Subjects (Part A) and Adults with Asthma on Medium to High Dose Inhaled Corticosteroids and Long-acting Beta-agonists (Part B)

20 Study Design

Part A of the study was a randomised, single-blinded, placebo-controlled study in male and female healthy volunteers to evaluate the safety, tolerability, PK, and immunogenicity of FAB1 by DPI administration (1 cohort in Sub Part A1 received IV FAB1).

Part A consisted of 4 sub parts (A1, A2, A3, and A4). The overall design of Part A is presented in Table 24.

Table 24 Study Design – Part A

Sub-parts	Population	Cohorts and treatments received
A1	Healthy volunteers	5 cohorts: SAD of 0.2 mg, 0.6 mg, 2 mg, 6 mg, and 16 mg of inhaled FAB1 or placebo
		1 cohort: Single 5 mg IV dose of FAB1 or placebo
A2	Healthy volunteers of Chinese and Japanese ethnicity	2 cohorts (1 Chinese cohort, and 1 Japanese cohort): Single 16 mg dose of inhaled FAB1 or placebo
A3	Healthy volunteers	3 cohorts: MAD of 2 mg, 6 mg, and 16 mg of inhaled FAB1 or placebo, once-daily for 14 days
A4	Healthy volunteers of Chinese and Japanese ethnicity	2 cohorts (1 Chinese cohort, and 1 Japanese cohort): highest dose in Sub-Part A3 of inhaled FAB1 or placebo, once-daily for 14 days.

MAD, multiple ascending dose; SAD, single ascending dose.

- 5 The primary objectives for Part A were the safety and tolerability of inhaled FAB1, and the PK and safety of IV FAB1. Secondary objectives were the PK of inhaled FAB1 (including participants of Japanese and Chinese ethnicity), and the immunogenicity of FAB1 following single and multiple dose administration.

Part B of the study was a randomised, double-blinded, placebo-controlled study in male and female adults with asthma on a combination of medium to high dose ICS plus LABA medications. Patients were
 10 randomised to one of 3 inhaled dose levels (0.4 mg, 2 mg, and 8 mg) of FAB1 or placebo, once daily by dry powder inhaler (DPI) administration, for 28 days in a parallel-group design.

The predicted dose to man following inhaled administration of FAB1 was based on two elements: First, the predicted human PK profile for FAB1 systemically and in the lung tissue, secondly, identification of a target lung concentration based on clinical efficacy data for tezepelumab. The clinical PK profile for FAB1
 15 was predicted using PK parameters which were allometrically scaled from cynomolgus monkeys. After inhaled administration, the average partition of FAB1 from lung to systemic circulation was estimated to be 2500 based on bronchial-alveolar lavage data from cynomolgus monkeys.

A target C_{trough} concentration in the lung was identified from a therapeutically efficacious systemic exposure of the systemic TSLP specific mAb (tezepelumab), with an assumed lung distribution coefficient
 20 from the serum. A calculated lung deposited dose of 1 mg (once daily) resulted in a C_{trough} concentration higher than the target concentration in lung tissue, corresponding to predicted average concentration (C_{ave}) in lung with 210 mg dose every 4 weeks of TSLP inhibiting systemic mAb, which has been proven to be efficacious in a Phase 3 study (Corren *et al. N Engl J Med* 2017: **377**: 936-946). Based on these

assumptions, delivered doses of 0.4, 2 and 8 mg (once daily over 28 days) were proposed in Part B of the study, with a decrease in FeNO as the primary outcome.

The primary objective was the safety and tolerability of inhaled FAB1 in patients with asthma on medium/high dose ICS/LABA. Secondary objectives were the PK and immunogenicity of inhaled FAB1, and the above mentioned effect on FeNO of inhaled FAB1 versus placebo, following once daily administration for 28 days.

Exploratory objectives were to evaluate the effect of FAB1 in multiple doses on lung function in asthma and on asthma symptoms and rescue medication/reliever therapy/use. Lung function measures were assessed by change from baseline in pre-bronchodilator (pre-BD) FEV₁ and FVC and post-bronchodilator (post-BD) FEV₁ and FVC. Asthma symptom measures were assessed by change from baseline in weekly ACQ-6 score.

For inclusion in the Part B study patients had to fulfil the following criteria:

1. Aged 18 to 75 years inclusive, with suitable veins for cannulation or repeated venipuncture.
2. Have a BMI between 18 and 35 kg/m² inclusive and weigh at least 45 kg.
3. Confirmed physician-led diagnosis of asthma for > 6 months before the Screening Visit. Patients must be on a stable combination of LABA and ICS total daily dose > 250 to 1000 µg fluticasone propionate DPI or equivalent for at least 1 month before the Screening Visit. If on asthma controller medications in addition to ICS plus LABA, the dose of the other asthma controller medications (xanthines, anticholinergics, leukotriene modifiers cromoglycate) must be stable for at least 4 weeks prior to screening visit.
4. Any of the following assessments within the last 10 years (documented in their medical history) to confirm variable airflow obstruction:
 - (a) Variability between clinic visits: FEV₁ > 12% and 200 mL.
 - (b) Response to 4 weeks' anti-inflammatory therapy: FEV₁ > 12% and 200 mL.
 - (c) Exercise challenge test: FEV₁ fall > 10% and 200 mL.
 - (d) Methacholine challenge test: FEV₁ ≥ 20% fall at < 8 mg/mL.
 - (e) Indirect challenge test (saline or mannitol): FEV₁ ≥ 15% fall.

Or in the screening period:

 - (f) Variability between clinic visits: FEV₁ > 12% and 200 mL.
 - (g) PEF_R for 2 weeks during run-in: PEF_R average daily variability > 10%.
5. Pre-bronchodilator FEV₁ ≥ 40% predicted at the Screening Visit in accordance with the ATS/ERS guidelines.
6. Have a FeNO of ≥ 30 ppb at the Screening Visit and ≥ 30 ppb at randomisation.
7. ACQ-6 score of ≥ 0.75 and ≤ 3.0 at screening.

8. During 7 consecutive days within Screening Period, demonstrates $\geq 65\%$ adherence (~4.5 days) to each of the following:

- (a) Twice daily home spirometry measurements
- (b) Twice daily entries in the eDiary (a compliant day comprises evening and subsequent morning diary entries).

5

Results

Study Populations

Part A

10 A total of 96 healthy volunteers were randomized and treated in Part A of the study; 72 received FAB1 and 24 received placebo. All completed the study except for 1 participant in the 6 mg once daily FAB1 cohort who was lost to follow-up. The median age was 33.5 (range: 20 to 55) years old, and the majority were male (94.4%). The majority were White (93.5%), 5.2% were Black or African American, and 1.3% were of other race. Baseline characteristics (height, weight, body mass index) were balanced across the treatment groups.

15 Part B

A total of 77 patients with asthma were randomized and treated in Part B of the study; 51 received FAB1 and 26 received placebo. All completed the study except for 1 patient in the 8 mg FAB1 cohort who withdrew consent. The median age was 52.0 (range: 21 to 75) years old, and 49.4% were male. The majority were White (93.5%), 5.2% were Black or African American, and 1.3% were of other race.

20 Baseline characteristics (height, weight, body mass index) were balanced across the treatment groups.

Pharmacokinetics

Part A

Following inhalation of single doses (0.2 to 16 mg), time to maximum serum concentration of FAB1 (t_{max}) was observed at a median time of 8.0 to 11.0 hours. FAB1 serum concentrations declined in the dose

25 range 2 mg to 16 mg with a geometric mean terminal half-life ($t_{1/2\lambda z}$) of 20.7 to 25.6 hours.

Interparticipant variability was high as judged by geometric mean percent coefficient of variation (%CV) for maximum plasma (peak) drug concentration after a given number of doses (N) before steady state is reached (C_{max}), area under the plasma concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), and area under plasma concentration-time curve from time 0 to infinity (AUC_{inf}).

30 There were no major differences in estimated PK parameters between Chinese/Japanese participants and non Asian participants.

Table 25 Geometric mean (%CV) PK Parameters of FAB1 Following Single DPI Dose Administration in Healthy Volunteers (Parts A1 and A2)

	SAD (Part A1)				Chinese and Japanese cohorts (Part A2)	
Parameter (Units)	Cohort 2 FAB1 0.6 mg once (N = 6)	Cohort 3 FAB1 2 mg once (N = 6)	Cohort 4 FAB1 6 mg once (N = 6)	Cohort 5 FAB1 16 mg once (N = 4)	Chinese cohort FAB1 16 mg once (N = 4)	Japanese cohort FAB1 16 mg once (N = 6)
AUC(0-24) (h*ng/mL)	17.66 (27.0) [n = 4]	26.88 (33.7) [n = 5]	95.17 (26.1) [n = 6]	273.0 (68.3) [n = 4]	230.4 (28.6) [n = 4]	262.9 (68.4) [n = 6]
AUClast (h*ng/mL)	11.02 (104.5) [n = 6]	31.94 (36.2) [n = 5]	158.2 (42.1) [n = 6]	568.2 (86.6) [n = 4]	412.9 (30.5) [n = 4]	501.3 (57.7) [n = 6]
AUCinf (h*ng/mL)	NC	NC	192.5 (47.4) [n = 5]	607.7 (82.4) [n = 4]	526.2 (21.7) [n = 3]	568.2 (57.8) [n = 6]
Cmax (ng/mL)	0.9844 (24.4) [n = 6]	1.321 (49.3) [n = 6]	5.721 (36.6) [n = 6]	14.57 (67.3) [n = 4]	11.96 (31.7) [n = 4]	15.05 (70.8) [n = 6]
tmax ^a (h)	11.07 (10.08- 12.10) [n = 6]	7.98 (5.98- 10.03) [n = 6]	8.88 (4.05- 24.00) [n = 6]	9.04 (8.00- 10.13) [n = 4]	8.96 (3.07- 10.35) [n = 4]	11.08 (4.00- 24.15) [n = 6]
t1/2λz (h)	NC	23.26 (46.7) [n = 4]	21.29 (46.7) [n = 5]	24.46 (27.4) [n = 4]	20.67 (24.6) [n = 3]	25.62 (25.3) [n = 6]

median (minimum – maximum).

DPI, dry powder inhaler; N, number of participants in treatment group; n, number of participants included in analysis; NC, not calculated.

- 5 %CV, percent coefficient of variation; AUC(0-24), area under the plasma concentration-time curve from time 0 to 24 hours; AUClast, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; Cmax, maximum plasma (peak) drug concentration after a given number of doses (N) before steady state is reached; t1/2λ, terminal elimination half-life; tmax, time to reach maximum concentration following drug administration of FAB1.

- 10 Following 14 days of daily doses of inhaled FAB1 at 2 mg, 6 mg and 16 mg, tmax of FAB1 was observed at a median time of 3.1 to 10.1 hours. At Day 14 serum concentrations declined with a geometric mean t1/2λz of 19.9 to 29.9 hrs in the dose range 2 mg to 16 mg. Upon repeated dosing, a 2- to 3-fold accumulation was observed in both AUC and Cmax and the systemic exposure generally increased in a dose-proportional manner. Interparticipant variability was high as judged by geometric mean %CV for Cmax, AUClast, and AUC(0-24). There were no major differences in estimated PK parameters in Chinese/Japanese participants and non-Asian participants following repeated dosing.

Table 26 Geometric mean (%CV) PK Parameters of FAB1 Following Multiple DPI Dose Administration in Healthy Volunteers, Sub-Part A3

Parameter (Units)	MAD (Part A3)						Chinese and Japanese cohorts (Part A4)			
	Cohort 1 FAB1 2 mg once daily (N = 6)		Cohort 2 FAB1 6 mg once daily (N = 5)		Cohort 3 FAB1 16 mg once daily (N = 6)		Chinese cohort FAB1 16 mg once daily (N = 6)		Japanese cohort FAB1 16 mg once daily (N = 5)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
AUC(0-24) (h*ng/mL)	37.24 (36.8) [n = 6]	77.58 (40.4) [n = 6]	100.2 (54.7) [n = 5]	280.9 (41.3) [n = 5]	265.2 (58.9) [n = 6]	773.4 (50.1) [n = 6]	246.7 (72.9) [n = 6]	600.9 (70.4) [n = 6]	247.5 (56.0) [n = 5]	484.2 59.0 [n = 5]
AUClast (h*ng/mL)	36.84 (37.0) [n = 6]	NC	99.59 (54.1) [n = 5]	NC	264.6§ (58.3) [n = 6]	NC	245.4 (73.3) [n = 6]	NC	247.0 (55.8) [n = 5]	NC
AUCinf (h*ng/mL)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Cmax(ng/mL)	2.161 (38.5) [n = 6]	4.413 (33.2) [n = 6]	5.816 65.5 [n = 5]	16.72 (46.0) [n = 5]	15.47 (57.7) [n = 6]	41.60 (47.7) [n = 6]	13.69 (70.9) [n = 6]	33.22 (73.4) [n = 6]	13.72 (57.9) [n = 5]	25.29 (41.2) [n = 5]
Ctrough (ng/mL)	NC	3.517 (45.5) [n = 6]	NC	12.25 (49.8) [n = 5]	NC	34.98 (46.3) [n = 6]	NC	23.19 (70.6) [n = 6]	NC	18.61 (66.7) [n = 5]
tmax ^a (h)	5.04 (3.95-12.03) [n = 6]	7.06 (2.88-10.12) [n = 6]	6.02 (3.00-10.05) [n = 5]	6.08 (3.98-10.28) [n = 5]	10.10 (8.00-23.70) [n = 6]	5.00 (0.00-24.00) [n = 6]	8.00 (3.00-11.97) [n = 6]	3.10 (1.50-9.83) [n = 6]	9.98 (3.10-23.70) [n = 5]	6.00 (3.00-12.02) [n = 5]
tl/2λz (h)	36.78 (47.8) [n = 5]	22.00 (42.9) [n = 6]	19.92 (28.2) [n = 3]	27.68 (35.3) [n = 5]	NC	27.85 (39.9) [n = 6]	NC	27.82 (24.0) [n = 6]	NC	29.88 (11.7) [n = 5]

	MAD (Part A3)						Chinese and Japanese cohorts (Part A4)			
Parameter (Units)	Cohort 1 FAB1 2 mg once daily (N = 6)		Cohort 2 FAB1 6 mg once daily (N = 5)		Cohort 3 FAB1 16 mg once daily (N = 6)		Chinese cohort FAB1 16 mg once daily (N = 6)		Japanese cohort FAB1 16 mg once daily (N = 5)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Rac AUC	NC	2.083 (33.1) [n = 6]	NC	2.805 (44.0) [n = 5]	NC	2.916 (30.5) [n = 6]	NC	2.436 (57.9) [n = 6]	NC	1.956 (54.2) [n = 5]
Rac Cmax	NC	2.042 (39.6) [n = 6]	NC	2.874 (43.6) [n = 5]	NC	2.689 (37.4) [n = 6]	NC	2.427 (52.1) [n = 6]	NC	1.843 (40.6) [n = 5]

^a median (minimum - maximum).
DPI, dry powder inhaler; N, number of participants included in analysis; NC, not calculated.

Part B

The PK of FAB1 has been characterised in both healthy volunteers (Part A) and in patients with asthma in Part B.

In healthy volunteers following 14 days of daily doses of inhaled FAB1 at 2 mg, 6 mg and 16 mg, and where a complete PK profile was generated, the observed Tmax of FAB1 was a median time of 5-7 hours (range 3-24 hours), with a geometric mean t1/2λz of 22-28 hours (range 14-45 hours) across the doses.

In patients following 28 days of daily doses of inhaled FAB1 at 0.4 mg, 2 mg and 8 mg, the observed Tmax of FAB1 was a median time of 6 to 8 hours (range 0.25-24 hours). After the last dose at Day 28 serum concentrations had not declined sufficiently within the sampling period in all subjects to characterise the t1/2λz using non-compartmental analysis, however in 4/24 subjects a geometric mean t1/2λz of 31 hrs in the 8 mg once daily dose regimen could be estimated (range 23-48 hours).

Upon repeated dosing, a 1- to 2.5-fold accumulation was observed in both AUC and Cmax and the systemic exposure generally increased in a dose-proportional manner. Interpatient variability was high as judged by geometric mean %CV for Cmax, AUClast, and AUC(0-24).

Based on the estimated PK parameters, it can be concluded that the PK of FAB1 is similar between healthy volunteers (Part A) and patients with asthma (Part B).

Table 27 Geometric mean (%CV) PK Parameters of FAB1 Following Multiple DPI Dose Administration in Patients with Asthma, Sub-Part B

Parameter (Units)	Cohort 1 0.4 mg once daily (N = 13)		Cohort 2 2 mg once daily (N = 13)		Cohort 3 8 mg once daily (N = 24)	
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
AUC(0-24) (h*ng/mL)	NC	24.05 (28.4) [n = 7]	36.17 (56.8) [n = 7]	75.66 (41.6) [n = 11]	86.49 (61.9) [n = 22]	238.0 (54.3) [n = 21]
AUClast (h*ng/mL)	10.70 (150.2) [n = 3]	NC	35.98 (58.0) [n = 7]	NC	86.95 (62.2) [n = 22]	NC
AUCinf (h*ng/mL)	NC	NC	NC	NC	NC	NC
Cmax (ng/mL)	1.138 (77.1) [n = 4]	1.022 (33.8) [n = 9]	1.514 (83.9) [n = 10]	3.616 (62.6) [n = 12]	4.768 (64.5) [n = 22]	12.09 (53.0) [n = 21]
tmax ^a (h) ^a	3.51 (2.00- 23.78) [n = 4]	7.82 (0.25- 24.00) [n = 9]	8.00 (3.92- 24.00) [n = 10]	6.00 (0.25- 24.00) [n = 12]	7.79 (2.00- 26.50) [n = 22]	7.58 (0.00- 24.00) [n = 21]
t1/2λz (h)	NC	NC	NC	NC	31.16 (60.1) [n = 3]	30.73 (14.0) [n = 4]

Parameter (Units)	Cohort 1 0.4 mg once daily (N = 13)		Cohort 2 2 mg once daily (N = 13)		Cohort 3 8 mg once daily (N = 24)	
	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28
Rac AUC	NC	1.93 (86.2)	NC	2.56 (70.6)	NC	2.67 (40.3)
Rac Cmax	NC	0.8836 (40.5) [n = 4]	NC	2.554 (63.1) [n = 10]	NC	2.438 (39.9) [n = 20]

Immunogenicity

Part A

In Part A, across the FAB1 groups the ADA prevalence (percentage of ADA evaluable participants who were ADA+ at any time) was 5.6% (4 of 71 evaluable participants), and the ADA incidence (percentage of ADA-evaluable participants who were TE-ADA+) was 1.4% (1 of 71 evaluable participants).

Part B

Immunogenicity prevalence and incidence rates in Part B of the study were low (Table). One patient in the 2 mg cohort had a treatment-induced ADA-positive response on Day 28 of treatment, and 1 patient in the 8 mg cohort had a treatment-induced ADA-positive on Days 14 and 28 of treatment.

Table 28 Anti-Drug Antibody results – Multiple Dose DPI in Patients with Asthma (Part B),

	FAB1 0.4 mg once daily (N = 13) n (%)	FAB1 2 mg once daily (N = 13) n (%)	FAB1 8 mg once daily (N = 25) n (%)	Pooled FAB1 (N = 51) n (%)
ADA prevalence ^a	0	1/13 (7.7)	1/25 (4.0)	2/51 (3.9)
ADA incidence ^b	0	1/13 (7.7)	1/25 (4.0)	2/51 (3.9)

^a Percentage of ADA-evaluable patients who were ADA positive at any time.

^b Percentage of ADA-evaluable patients who were treatment-induced or treatment boosted ADA positive.

Percentages are based on the number of ADA-evaluable patients (patients with at least 1 ADA

assessment).

Pharmacodynamics

After 28 days of treatment, there was a numerical reduction in FeNO levels across all FAB1 cohorts (Table). FAB1 treatment reduced levels of FeNO as early as 6 hours post-dose in the 0.4 mg cohort and Day 7 in the 2 mg and 8 mg cohorts, and the reduction was sustained throughout 28 days (**Error! Reference source not found.**). Although only the comparison between FAB1 8 mg and placebo cohorts was statistically powered, a statistically significant reduction in FeNO level was found in FAB1 8 mg and 0.4 mg cohorts. A 23% reduction (geometric mean ratio 0.77; 1-sided p-value = 0.0369) and 46%

reduction (geometric mean ratio 0.54; 1-sided p-value = 0.0003) in FeNO levels were observed for 8 mg and 0.4 mg, respectively, compared to placebo.

Table 29 Change from baseline in the FeNO level at Day 28 – Part B (Pharmacodynamic Analysis Set)

	Treatment			FAB1 versus placebo		
	n	Geometric LS means	80% CI	Geometric mean ratio	80% CI of ratio	p-value
FAB1 0.4 mg	13	0.4322	(0.3616, 0.5166)	0.5437	(0.4363, 0.6774)	0.0003
FAB1 2 mg	13	0.6429	(0.5376, 0.7689)	0.8087	(0.6488, 1.008)	0.1083
FAB1 8 mg	22	0.6124	(0.5354, 0.7005)	0.7703	(0.6396, 0.9278)	0.0369
Placebo	25	0.7950	(0.6991, 0.9040)	NA		

- 5 The change from baseline in FeNO level was analysed using MMRM with treatment group, baseline FeNO, visit, treatment-by-visit interaction as fixed effect and patient as random-effect. Analyses was performed on the log-transformed FeNO data (change from baseline and percentage change) to normalise the skewed distribution of this endpoint and result back-transformed to linear scale. The within-patient correlation was modeled using the unstructured covariance matrix. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was performed using only the OC without imputation of missing values. A REML method was used for estimation. Treatment effect was estimated using contrasts of the LS means on the correspondent treatment by-day interaction, along with 2-sided 80% CI and 1-sided test for the p-value corresponding to the between-treatment group difference. One patient was excluded from due to incompatible FeNO data in CRF, and 2 patients were excluded due to important protocol deviation.
- 10
- 15 CI, confidence interval; FeNO, fractional exhaled nitric oxide; LS, least squares; n, number of patients in a given category.

There was also a numerical improvement in lung function after 28 days of treatment as evidenced by clinic based pre-BD FEV₁ compared to placebo (105 ml at week 4 at highest dose – Table 30 and Figure 26)

Table 30 Change (ml) from baseline in the clinic pre-BD FEV₁ at Day 28 – Part B

	FEV ₁ change from baseline compared to placebo (1h PSOI)	FEV ₁ change from baseline compared to placebo (D2)	FEV ₁ change from baseline compared to placebo (D7)	FEV ₁ change from baseline compared to placebo (D14)	FEV ₁ change from baseline compared to placebo (D28)
FAB1 0.4 mg (n=13)	- 18 ml [0.43]	+ 84 ml [0.20]	+ 47 ml [0.34]	- 27 ml [0.38]	- 6 ml [0.48]

	FEV ₁ change from baseline compared to placebo (1h PSOI)	FEV ₁ change from baseline compared to placebo (D2)	FEV ₁ change from baseline compared to placebo (D7)	FEV ₁ change from baseline compared to placebo (D14)	FEV ₁ change from baseline compared to placebo (D28)
FAB1 2 mg (n=12)	+ 190 ml [0.03]	+ 193 ml [0.03]	+ 111 ml [0.17]	+ 120 ml [0.11]	+ 9 ml [0.47]
FAB1 8 mg (n=21)	+ 152 ml [0.03]	+ 270 ml [0.0009]	+ 151 ml [0.06]	+ 113 ml [0.09]	+ 105 ml [0.14]

PSOI = post-start of inhalation; n=number of subjects (D28 figure); numbers in square brackets denote p-value

In addition, there was as a numerical improvement in ACQ-6 symptoms (Figure 27).

EXAMPLE 8 – Population PK model

- 5 A population PK (popPK) model was developed to quantify the variability in observed clinical PK data and to understand any differences in population between those in Part 1A in healthy adult volunteers, and Part 1B in asthmatic adult patients on medium/high doses of inhaled corticosteroids/long acting beta2 agonists (NCT05110976). The popPK model had four compartments defined with a combined zero order and first order absorption of the administered dose in the lung, and observations defined by the dotted
- 10 line in the serum of FAB1 (Figure 28). Briefly, the IV and Part 1A single ascending dose data were used to estimate bioavailabilities for each absorption type, which were then fixed in the subsequent multiple ascending dose popPK model which included the individuals from Part 1A and Part 1B. The popPK model was simulated ($n=1000$ per dose) to obtain predictions and prediction intervals of serum concentrations (Figure 29 dashed lines) and scaled to a predicted lung concentration (Figure 29 solid lines) for Part 1B in
- 15 patients at 0.4, 2 and 8 mg (once daily for 28 days).

Dose selection for Phase 2

- The observed PK profile in Phase 1 (both in patients and healthy volunteers) was well aligned with the predicted clinical profile building confidence in the exposure assumption in relation to inhaled doses of FAB1. Predicted lung concentrations following the anticipated therapeutic dose of 2 mg were expected to
- 20 be above the target level based on average exposure related to an efficacious dose of 210 mg QW4 of tezepelumab (Figure 29). Further on a positive proof of mechanism with significant reduction of FeNO in asthmatic patients after inhaled administration of 8 mg QD of FAB1 provided the clinical relevance of TSLP inhibition in lung and confidence in dose range (0.4 - 8 mg) selected for Phase 2.

EXAMPLE 9 – Phase 2b, randomised, double-Blind, placebo-controlled dose range-finding study to assess efficacy and safety of 3 dose levels of inhaled FAB1

This example describes a Phase 2b, randomised, double-Blind, placebo controlled dose range finding study to assess efficacy and safety of 3 dose levels of inhaled FAB1 (8 mg, 2 mg, 0.4 mg) given once daily via inhalation for 12 to 52 weeks in adults.

Patient Population

The study will include adults (N = 516, approximately) with documented physician-diagnosed asthma for a minimum of 12 months duration, a history of ≥ 1 severe exacerbation within the last 12 months All participants will be symptomatic (asthma control questionnaire [ACQ] score ≥ 1.5) on background asthma therapy of medium or high dose ICS (as per GINA 2023 report) in combination with LABA $\pm$ an additional non-biologic controller therapy (GINA step 4 or 5 therapy).

The target population includes severe asthma, similar to the tezepelumab clinical program, but expands to include moderate disease. Approximately 30% will have had 1 exacerbation in the last 12 months (defined as: asthma worsening which results in OCS use for ≥ 3 days, hospitalization or ER visit which results in systemic CS use) and approximately 70% of patients will have had ≥ 2 severe exacerbations within the last 12 months.

Study Design

Eligible patients will be randomised 1:1:1:1 to FAB1 8 mg once daily, 2 mg once daily, 0.4 mg once daily or placebo. The range of doses in the Phase IIb study is based on results from the Phase I, Part b study, where these same 3 doses (8 mg, 2 mg, and 0.4 mg) were explored against placebo.

The study is of variable length with a 12-week treatment period and an optional safety extension of up to 52 weeks of total dosing. The safety extension component will end when the final patient enrolled to the study completes 12 weeks of treatment. The study design is provided in Figure 30.

Primary and secondary endpoints are provided in **Error! Reference source not found..**

Table 31 - Objectives & Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of FAB1 as compared to placebo on time to first CompEx asthma event in patients with uncontrolled moderate to severe asthma	Time to first CompEx asthma event
Secondary	

To evaluate the effect of FAB1 as compared to placebo on lung function	Change from baseline of: 1. Pre-BD FVC: Weeks 1, 4 and 12 2. Post-BD FVC: Week 12 3. Pre-BD FEV1: Weeks 1, 4 and 12 4. Post-BD FEV1: Week 12 5. Weekly mean morning PEF: Weeks 1, 4, 6, 8, 10 and 12 6. Weekly mean evening PEF: Weeks 1, 4, 6, 8, 10 and 12
To evaluate the effect of FAB1 as compared to placebo on asthma symptoms and control	Change from baseline: 1. Weekly mean asthma symptom diary score, Weeks 1, 4, 6, 8, 10 and 12 2. ACQ-6: baseline, Weeks 2, 4, 8, 12 and over the treatment period 3. AQLQ: baseline, Weeks 4, 8 and 12 4. SGRQ: baseline and week 12
To evaluate the effect of FAB1 as compared with placebo on asthma-related biomarkers	Change from baseline: 1. FeNO: Weeks 1, 4, 8 and 12 2. Blood eosinophils, Weeks 1, 4, 8 and 12 3. IgE, Weeks 1, 4, 8 and 12
To evaluate the PK of FAB1 and ADA	FAB1 and anti-drug antibody (ADA) plasma concentrations: pre-dose at baseline, Weeks 4, 8 and 12

Primary Endpoint

The CompEx Asthma is a composite endpoint that allows evaluation of treatment effect on exacerbation involving fewer participants compared with severe exacerbations. There are two main types of CompEx

5 Asthma events:

- Severe exacerbations of asthma
- Diary-based (objective deterioration)

Severe exacerbations of asthma CompEx events

Asthma exacerbations will be evaluated by the investigator at each visit. Severe exacerbations are
10 defined as those episodes that lead to hospitalisation, emergency room visit, and/or treatment with oral glucocorticosteroid as detailed below:

- Inpatient hospitalization: an admission to an inpatient facility and/or evaluation and treatment in healthcare facility for ≥ 24 hours due to asthma.
- Emergency room or urgent care visit: evaluation and treatment for < 24 hours in an emergency
15 department or urgent care centre due to asthma required systemic corticosteroids.

- Use of a temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.

5 Diary-based CompEx events

Diary-based CompEx events are based on patient-reported deteriorations in three e-Diary variables, captured twice daily (morning and evening). This combination results in 6 different e-Diary variables.

Diary-based CompEx events are defined by threshold and slope criteria using the following Morning/Evening e-Diary variables:

- 10
 - Peak expiration flow (PEF - morning [PEFm] and evening [PEFe])

PEF (L/min) is a home spirometry measure. The capture of PEF follows standardized procedures. During data collection, all required attempts (usually three) are recorded. Only the best of the three attempts (max PEF) is included in the diary dataset and should be used in calculating CompEx events.
- 15

PEFm measurements are conducted at home by the patient, with the exception of site visit days. On a site visit day, the patient performs PEF assessment on-site, and the home PEFm data might not be available. PEFm cannot be imputed with site PEF measurements from on-site visit days (this is because PEFm is patient-reported data and site PEF is investigator-reported data and these two data sources cannot be used interchangeably in CompEx calculations).
- 20
 - Symptom score (0-3) (morning [Sm] and evening [Se])

Asthma symptom scores during night-time and day-time will be assessed by the patient each morning and evening according to the following scoring system:

0: You have no asthma symptoms.

1: You are aware of your asthma symptoms, but you can easily tolerate the symptoms.
- 25

2: Your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep).

3: You are unable to do your normal activities (or to sleep) because of your asthma.

 - Use of rescue medication (number of doses) (morning [Rm] and evening [Re])

Rescue medication use is measured by the number of puffs taken of SABA used during the study.
- 30

The number of doses of rescue medication is defined as the number of puffs of inhaler recorded in the morning (for preceding night) and evening (for preceding day), respectively. If a nebulizer is used in a study, the number of doses of reliever medication use is defined as the number of puffs of inhaler plus twice the number of nebulizer applications.

Determination of Diary-based (Objective Deterioration) CompEx events

The e-Diary events are based on deteriorations in the e-Diary variables PEF_m, PEF_e, S_m, S_e, R_m and R_e as defined above. Diary-based CompEx Asthma events can be of two types based on:

- Threshold criteria
- 5 • Threshold and slope criteria.

A participant will be considered to have a CompEx event during the planned treatment period if the participant has one or both of the following:

- An objective deterioration, which is defined as either the threshold criterion
- or
- 10 • The slope criterion (or both), as defined below, being met for ≥ 2 consecutive days.

For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For the e-Diary data (which is captured twice during the day), one day will be defined by the morning/evening pairing for consistency with published precedent for the CompEx endpoint. (Note: other e-Diary endpoints in this study will use an evening/morning pairing to

15 define one day.) The morning e-Diary recordings captured on the first day of treatment will not be included in the calculation of the CompEx endpoint.

Baseline for diary-based variables

Before threshold and slope criteria are assessed, baseline values need to be calculated for each of the six diary-based variables: PEF_m, PEF_e, S_m, S_e, R_m and R_e. Baseline values will be calculated for each

20 individual patient as the average of the variable during the last ten days of the Run-in Period (days -10 to -1 with day -1 denoting the day before randomisation). In the event that less than 10 days of data is available, at least 5 days of data is required to calculate the baseline values.

CompEx Asthma events cannot be calculated for participants with missing baseline diary-based variables.

25 Threshold criteria CompEx Asthma event:

- a. PEF_m or PEF_e $\geq 15\%$ decrease from baseline in either morning or evening home-based PEF, and at least one of the following:
- b. R_m or R_e ≥ 1.5 doses increase from baseline in rescue medication in either the morning (for preceding night) or evening (for preceding day)
- 30 c. S_m or S_e ≥ 1 score increase from baseline in symptom score or achieving the absolute maximal symptom score (3), in either the morning or evening. This means the criterion is also met when the value is at the highest on the symptom score 3.

For (b), the number of doses of rescue medication is defined as the number of puffs of inhaler recorded in the morning and evening, respectively.

Assessment of the threshold criteria in any rolling 2-day consecutive period will be based on the available data during that period. The threshold criteria can be met with non-missing values for fewer than the six variables specified above, provided those non-missing values meet the criteria. In other words, this gives a total of eight variable combinations: PEFm-Rm, PEFm-Re, PEFm-Rm, PEFm-Re and PEFm-Sm, PEFm-Se, PEFm-Sm, and PEFm-Se, where the deterioration criteria need to be fulfilled for both variables in at least one combination for at least 2 consecutive days.

Threshold and slope criteria CompEx Asthma event:

A threshold and slope criteria CompEx Asthma event is when: (a), (b) or (c) of the threshold criteria above is met for at least 2 consecutive days and the regression slope requirement over the preceding 5 days is also met. Note that a CompEx event is never based on slope criteria only.

The regression slope requirement in the preceding 5 days is that all of the following are met:

- PEFm slope $\leq -3\%/day$
- PEFm slope $\leq -3\%/day$
- Rm slope ≥ 0.3 doses/day
- Re slope ≥ 0.3 doses/day
- Sm slope ≥ 0.2 score/day
- Se slope ≥ 0.2 score/day.

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the absolute values of each of the six variables separately against day number, with no other variables included in the model.

For PEFm and PEFm, the regression slope thus obtained will first also be divided by the baseline PEFm and PEFm value and multiplied by 100 respectively before applying the above criteria.

A regression slope will be calculated provided there are at least two non-missing values in the required 5 days. If one or more of the six variables above does not have at least two non-missing values in the required 5 days, then the slope requirement cannot be met.

Duration of diary-based CompEx Asthma events

The start date of a CompEx Asthma event is defined as the earliest of the exacerbation or objective deterioration start dates which meets the definition. Objective deterioration start date is defined as the earliest Day 1 from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criteria.

The end date of a CompEx event is defined as the latest of the exacerbation or objective deterioration end dates which meets the definition. Objective deterioration end date is defined as the latest from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criteria.

Whether or not diary-based CompEx criteria are met, is evaluated by a rolling window, with each pair of two consecutive days evaluated for fulfilment of the criteria. This also applies if different consecutive days fulfil different types of criteria (threshold only or threshold and slope).

Combining CompEx Asthma events

- 5 If the end date of the first CompEx event and the start date of the second CompEx event are less than 7 days apart for any participant, then these will be counted as one CompEx event.

Claims:

1. A pharmaceutical composition comprising spray-dried particles, the spray-dried particles comprising:
 - a. about 5% (w/w) to about 15% (w/w) leucine;
 - b. about 1% (w/w) to about 5% (w/w) trileucine;
 - c. about 1% (w/w) to about 10% (w/w) histidine buffer at a pH of between about pH 5 to pH 6;
 - d. about 1% (w/w) to about 80% (w/w) of an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody; and
 - e. a glass stabilisation agent.
2. The pharmaceutical composition according to claim 1, comprising about 1% (w/w) to about 3% (w/w) trileucine.
3. The pharmaceutical composition according to claim 2, comprising about 2% (w/w) trileucine.
4. The pharmaceutical composition according to any of claims 1 to 3, comprising about 8% (w/w) to about 12% (w/w) leucine.
5. The pharmaceutical composition according to claim 4, comprising about 10.5% (w/w) leucine.
6. The pharmaceutical composition according to any of claims 1 to 5, comprising about 1% (w/w) to about 5% (w/w) histidine buffer.
7. The pharmaceutical composition according to claim 6, comprising about 2.5% (w/w) to about 3.5% (w/w) histidine buffer.
8. The pharmaceutical composition according to claim 7, comprising about 3.14% (w/w) histidine buffer.
9. The pharmaceutical composition according to claim 1, wherein the antigen binding fragment is present at a concentration of about 2% (w/w).
10. The pharmaceutical composition according to claim 1, wherein the antigen binding fragment is present at a concentration of about 10% (w/w).
11. The pharmaceutical composition according to claim 1, wherein the antigen binding fragment is present at a concentration of about 40% (w/w).
12. The pharmaceutical composition according to any of claims 1 to 11, wherein the antigen binding fragment comprises:
 - a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
 - e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.

13. The pharmaceutical composition according to any of claims 1 to 11, wherein the antigen binding fragment comprises:
- a. a HCDR1 having the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 having the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 having the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 having the amino acid sequence of SEQ ID NO: 5;
 - e. a LCDR2 having the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 having the amino acid sequence of SEQ ID NO: 7.
14. The pharmaceutical composition according to any of claims 1 to 13, wherein the antigen binding fragment comprises a VH domain comprising a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 4 and a VL domain comprising a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 8.
15. The pharmaceutical composition according to any of claims 1 to 14, wherein the antigen binding fragment comprises a VH domain comprising the sequence of SEQ ID NO: 4; and a VL domain comprising the sequence of SEQ ID NO: 8.
16. The pharmaceutical composition according to any of claims 1 to 15, wherein the antigen binding fragment is a Fab, Fab', F(ab')₂, scFv, minibody or diabody.
17. The pharmaceutical composition according to claim 16, wherein the antigen binding fragment is a Fab.
18. The pharmaceutical composition according to claim 17, wherein the Fab is of an IgG1 antibody.
19. The pharmaceutical composition according to claim 18, wherein the antigen binding fragment comprises a first sub-unit having the sequence set forth in SEQ ID NO: 28 and a second sub-unit having the sequence set forth in SEQ ID NO: 29.
20. The pharmaceutical composition according to any of claims 1 to 19, wherein the glass stabilization agent is selected from trehalose, sucrose, raffinose, inulin, dextran, mannitol, and cyclodextrin.
21. The pharmaceutical composition according to claim 20, wherein the glass stabilization agent is trehalose.
22. The pharmaceutical composition according to claim 21, wherein the trehalose is at a percent (w/w) concentration to make up to about 100%.
23. The pharmaceutical composition according to any of claims 1 to 22, wherein the composition does not comprise a surfactant.
24. The pharmaceutical composition according to any of claims 1 to 23, comprising:
- a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;

- 5 d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 15 h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- 15 i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
25. The pharmaceutical composition according to any of claims 1 to 24, wherein, following reconstitution, the number of sub-visible particles between 5 μ m to 200 μ m is less than about 2.5×10^4 /ml.
26. The pharmaceutical composition according to claim 25, wherein, following reconstitution, the number of sub-visible particles between 5 μ m to 200 μ m is less than about 0.5×10^4 /ml.
27. The pharmaceutical composition according to any of claims 1 to 26, wherein, following reconstitution, the number of sub-visible particles between 10 μ m to 200 μ m is less than about 1×10^4 /ml.
28. The pharmaceutical composition according to claim 27, wherein, following reconstitution, the number of sub-visible particles between 10 μ m to 200 μ m is less than about 0.2×10^4 /ml.
29. The pharmaceutical composition according to any of claims 1 to 28, wherein, following reconstitution, the number of sub-visible particles between 25 μ m to 200 μ m is less than about 2×10^3 /ml.
30. The pharmaceutical composition according to claim 29, wherein, following reconstitution, the number of sub-visible particles between 25 μ m to 200 μ m is less than about 0.2×10^3 /ml.
31. The pharmaceutical composition according to any of claims 24 to 30, wherein the number of sub-visible particles is determined by dynamic flow imaging microscopy, optionally by microflow imaging (MFI).
32. The pharmaceutical composition according to any of claims 24 to 31, wherein the number of sub-visible particles is determined following reconstitution in water, to an antigen-binding fragment concentration of either 2.5 mg/ml or 30 mg/ml.
33. A process for making a pharmaceutical composition for inhalation, comprising:

- a. Providing an aqueous solution of about pH 5 to about pH 6 comprising leucine, trileucine, histidine, a glass stabilization agent and an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody;
 - b. Spray drying the aqueous solution of (a) to produce dry powder particles; and
 - c. Collecting the dry powder particles;
- wherein the aqueous solution comprises about 5% (w/w) to about 15% (w/w) leucine, about 1% (w/w) to about 5% (w/w) trileucine, about 1% (w/w) to about 10% (w/w) histidine, about 5% (w/w) to about 50% (w/w) antigen binding fragment and % (w/w) glass stabilization agent to 100% total solids content.
34. The process according to claim 33, wherein the aqueous solution has a pH of 5.5.
 35. The process according to any of claims claim 33 to 34, wherein the glass stabilization agent is trehalose.
 36. The process according to claim 33 to 35, wherein the aqueous solution comprises:
 - a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
 - i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
 37. A dry powder formulation obtained by the process of any of claims 33 to 36.
 38. A method of treating a TSLP-related condition in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37.
 39. The pharmaceutical composition according to any of claims 1 to 32 or the dry powder formulation of claim 36 for use in treating a TSLP-related condition.

40. Use of the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37 in the manufacture of a medicament for the treatment of a TSLP-related condition.
- 5 41. The method of claim 38, composition for use according to claim 39, or use according to claim 40, wherein the TSLP-related condition is asthma, COPD, allergic rhinitis, allergic rhinosinusitis, allergic conjunctivitis, eosinophilic esophagitis, chronic spontaneous urticaria or chronic rhinosinusitis.
42. The method, use, or composition for use according to claim 41, wherein the TSLP-related condition is asthma.
- 10 43. The method, use, or composition for use according to claim 41, wherein the TSLP-related condition is COPD.
44. A method for improving lung function in a subject with asthma or COPD, comprising administering to the subject the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37.
- 15 45. The pharmaceutical composition according to any of claims 1 to 32 or the dry powder formulation of claim 37 for use in a method of improving lung function in a subject with asthma or COPD.
46. Use of the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37 in the manufacture of a medicament for improving lung function in a subject with asthma or COPD.
- 20 47. The method, use, or composition for use according to any of claims 44 to 46, wherein improving lung function means one or more of the following parameters: improvement compared to baseline of (i) pre-bronchodilator (BD) FVC, (ii) post-BD-FVC, (iii) pre-BD-FEV₁, (iv) post-BD FEV₁, (v) mean morning PEF and/or (vi) mean evening PEF.
48. The method, use, or composition for use according to claim 47, wherein improvement means achieving the minimum clinical important difference for each respective parameter.
- 25 49. The method, use, or composition for use according to claim 48, wherein baseline refers to the value of the respective parameter prior to commencement of the treatment with the pharmaceutical composition or the dry powder formulation.
50. The method, use, or composition for use according to claim 49 wherein prior means within one month of the commencement of the treatment.
- 30 51. The method, use, or composition for use according to claim 49 or 50, wherein the improvement compared to baseline of pre-BD-FEV₁ is at least 5 ml, at least 10 ml, at least 15 ml, at least 20 ml, at least 25 ml, at least 30 ml, at least 35 ml, at least 40 ml, at least 45 ml, at least 50 ml, at least 55 ml, at least 60 ml, at least 65 ml, at least 70 ml, at least 75 ml, at least 80 ml, at least 85 ml, at least 90 ml, at least 95 ml, at least 100 ml, at least 105 ml, at least 110 ml, at least 115 ml, at least 120 ml, at least 125 ml, at least 130 ml, at least 135 ml, at least 140 ml, at least 145 ml, at least 150 ml, at least 160 ml, at least 170 ml, at least 180 ml, at least 190 ml, at least 200 ml, at least 210 ml, at least 220 ml, at least 230 ml, at least 240 ml or at least 250 ml.
- 35

52. The method, use, or composition for use according to claim 49 or 50, wherein the improvement compared to baseline of pre-BD- FEV_1 is at least 80 ml at day 2 after commencement of treatment, at least 45 ml or at least 100 ml at day 7 after commencement of treatment, at least 100 ml at day 14 after commencement of treatment, or at least 5 ml or at least 100 ml at day 28 after commencement of treatment.
53. A method for improving symptoms of asthma or COPD in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37.
54. The pharmaceutical composition according to any of claims 1 to 32 or the dry powder formulation of claim 37 for use in a method of improving symptoms of asthma or COPD in a subject in need thereof.
55. Use of the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37 in the manufacture of a medicament for improving symptoms of asthma or COPD in a subject in need thereof.
56. The method, use, or composition for use according to any of claims 53 to 55, wherein improving symptoms of asthma means one or more of the following parameters: improvement compared to baseline (i) mean asthma symptom diary score, (ii) ACQ-6 score, (iii) AQLQ score, and/or (iv) SGRQ score.
57. The method, use, or composition for use according to any of claims 56, wherein improving symptoms of asthma means an improvement compared to baseline of ACQ-6 score.
58. The method, use, or composition for use according to any of claims 53 to 57, wherein improvement means achieving the minimum clinical important difference (MCID) for each respective score.
59. The method, use, or composition for use according to claim 56 or 57, wherein baseline refers to the value of the respective score prior to commencement of the treatment with the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37.
60. The method, use, or composition for use according to claim 59 wherein prior means within one month of the commencement of the treatment.
61. The method, use, or composition for use according to claim 42 or any of claims 44 to 60, wherein the asthma is moderate to severe asthma.
62. The method, use, or composition for use according to claim 42 or any of claims 44 to 61, wherein the pharmaceutical composition is administered by inhalation or intranasally.
63. The method, use, or composition for use according to claim 42 or any of claims 44 to 62, wherein the pharmaceutical composition is delivered by dry powder inhaler.
64. The method, use, or composition for use according to claim 42 or any of claims 44 to 63, wherein the pharmaceutical composition is administered or to be administered at a dose comprising about 0.4 mg to about 8 mg of the antigen binding fragment.

65. The method, use, or composition for use according to any of claims 64, wherein the dose is administered or to be administered daily.
66. The method, use, or composition for use according to any of claims 65, wherein the dose is administered or to be administered once daily (Q1D).
- 5 67. The method, use, or composition for use according to any of claims 64 to 66, wherein the pharmaceutical composition is administered or to be administered at a dose comprising about 0.4 mg of the antigen binding fragment.
68. The method, use, or composition for use according to any of claims 64 to 66, wherein the pharmaceutical composition is administered or to be administered at a dose comprising about 2
10 mg of the antigen binding fragment.
69. The method, use, or composition for use according to any of claims 64 to 66, wherein the pharmaceutical composition is administered or to be administered at a dose comprising about 8 mg of the antigen binding fragment.
70. The method, use, or composition for use according to claim 42 or any of claims 44 to 69, wherein
15 the asthma is uncontrolled moderate to severe asthma.
71. The method, use, or composition for use according to claim 42 or any of claims 44 to 70, wherein the subject has a history of ≥ 1 severe exacerbation within the last 12 months prior to the treatment.
72. The method, use, or composition for use according to claim 42 or any of claims 44 to 71, wherein the subject has a history of ≥ 2 severe exacerbations within the last 12 months prior to the
20 treatment.
73. The method, use, or composition for use according to claim 42 or any of claims 44 to 72, wherein the subject is co-administered a background therapy.
74. The method, use, or composition for use according to claim 73, wherein the subject is already receiving the background therapy prior to the treatment.
- 25 75. The method, use, or composition for use according claim 73 or 74, wherein the background therapy is selected from: inhaled corticosteroids, Leukotriene modifiers, long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), combination therapies such as Fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol and fluticasone and vilanterol, theophylline, short-acting beta agonists (SABAs), ipratropium or a combination of ipratropium and
30 albuterol or oral corticosteroids.
76. The method, use, or composition for use according to any of claims 73 to 75, wherein the background therapy comprises medium or high dose ICS (as per GINA 2023 report) in combination with LABA (GINA step 4 or 5 therapy).
77. The method, use, or composition for use according to any of claims 38 to 76, wherein the subject
35 has a baseline blood eosinophil count of ≥ 150 cells/ μ l.
78. The method, use, or composition for use according to any of claims 38 to 77, wherein the subject has a baseline blood eosinophil count of ≥ 300 cells/ μ l.

79. The method, use, or composition for use according to claim 77 or 78, wherein baseline refers to the blood eosinophil count prior to commencement of the treatment.
80. The method, use, or composition for use according to claim 79, wherein prior means within one month of the commencement of the treatment.
- 5 81. The method, use, of composition for use according to any of claims 38 to 80, wherein, following treatment with the pharmaceutical composition of any of claims 1 to 32 or the dry powder formulation of claim 37, the ADA prevalence in the subject is less than 6%, less than 5% or less than 4%, and/or the ADA incidence is less than 4%, less than 3% or less than 2%.
- 10 82. A method of treating asthma in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody, wherein the pharmaceutical composition is administered once daily (Q1D) by inhalation.
- 15 83. A pharmaceutical composition for use in a method of treating asthma in a subject in need thereof, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody that is to be administered to the subject one daily (Q1D) by inhalation.
- 20 84. Use of an antigen binding fragment of an anti-TSLP-antibody in the manufacture of a pharmaceutical composition for the treatment of asthma by inhalation, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of the antigen binding fragment.
- 25 85. A method of treating asthma in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody, wherein the pharmaceutical composition is administered once daily (Q1D) by inhalation and wherein the antigen binding fragment is a Fab comprising:
- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
 - e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.
- 30 86. A pharmaceutical composition for use in a method of treating asthma in a subject in need thereof, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody that is to be administered to the subject once daily (Q1D) by inhalation, wherein the antigen binding fragment is a Fab comprising:
- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
 - e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.
- 35 40

87. Use of an antigen binding fragment of an anti-TSLP-antibody in the manufacture of a pharmaceutical composition for the treatment of asthma, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of the antigen binding fragment, wherein the antigen binding fragment is a Fab comprising:
- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
 - e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7,
- and the pharmaceutical composition is to be administered once daily (Q1D) by inhalation.
88. The method, use, or pharmaceutical composition for use according to any of claims 82 to 87, wherein the antigen binding fragment comprises a VH domain having a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 4 and a VL domain having a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 8.
89. The method, use, or pharmaceutical composition for use according to any of claims 82 to 88, wherein the antigen binding fragment comprises a VH domain comprising the sequence of SEQ ID NO: 4; and a VL domain comprising the sequence of SEQ ID NO: 8.
90. The method, use, or pharmaceutical composition for use according to any of claims 82 to 89, wherein the Fab is of an IgG1 antibody.
91. The method, use, or pharmaceutical composition for use according to claim 90, wherein the antigen binding fragment comprises a first sub-unit having the sequence set forth in SEQ ID NO: 28 and a second sub-unit having the sequence set forth in SEQ ID NO: 29.
92. The method, use, or pharmaceutical composition for use according to any of claims 82 to 91, wherein the pharmaceutical composition comprises spray-dried particles comprising:
- g. about 5% (w/w) to about 15% (w/w) leucine;
 - h. about 1% (w/w) to about 5% (w/w) trileucine;
 - i. about 1% (w/w) to about 50% (w/w) of an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody;
 - j. a buffer; and
 - k. a glass stabilisation agent.
93. The method, use, or pharmaceutical composition for use according to claim 92, comprising about 1% (w/w) to about 10% (w/w) histidine buffer at a pH of between about pH 5 to pH 6.
94. The method, use, or pharmaceutical composition for use according to claims 92 or 93, comprising about 1% (w/w) to about 3% (w/w) trileucine.
95. The method, use, or pharmaceutical composition for use according to claims 94, comprising about 2% (w/w) trileucine.

96. The method, use, or pharmaceutical composition for use according to any of claims 92 to 95, comprising about 8% (w/w) to about 12% (w/w) leucine.
97. The method, use, or pharmaceutical composition for use according to claim 96, comprising about 10.5% (w/w) leucine.
- 5 98. The method, use, or pharmaceutical composition for use according to any of claims 92 to 97, comprising about 1% (w/w) to about 5% (w/w) histidine buffer.
99. The method, use, or pharmaceutical composition for use according to claim 98, comprising about 2.5% (w/w) to about 3.5% (w/w) histidine buffer.
- 10 100. The method, use, or pharmaceutical composition for use according to claim 99, comprising about 3.14% (w/w) histidine buffer.
101. The method, use, or pharmaceutical composition for use according to any of claims 92 to 100, wherein the antigen binding fragment is present at a concentration of about 2% (w/w), about 10% (w/w) or about 40% (w/w).
- 15 102. The method, use, or pharmaceutical composition for use according to any of claims 92 to 101, wherein the antigen binding fragment is present at a concentration of about 2% (w/w).
103. The method, use, or pharmaceutical composition for use according to any of claims 92 to 102, wherein the antigen binding fragment is present at a concentration of about 10% (w/w).
104. The method, use, or pharmaceutical composition for use according to any of claims 92 to 103, wherein the antigen binding fragment is present at a concentration of about 40% (w/w).
- 20 105. The method, use, or pharmaceutical composition for use according to any of claims 92 to 104, wherein the glass stabilization agent is selected from trehalose, sucrose, raffinose, inulin, dextran, mannitol, and cyclodextrin.
106. The method, use, or pharmaceutical composition for use according to claim 105, wherein the glass stabilization agent is trehalose.
- 25 107. The method, use, or pharmaceutical composition for use according claim 106, wherein the trehalose is at a percent (w/w) concentration to make up to about 100%.
108. The method, use, or pharmaceutical composition for use according to any of claims 92 to 107, wherein the composition does not comprise a surfactant.
- 30 109. The method, use, or pharmaceutical composition for use according to any of claims 92 to 108, comprising:
- a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
 - 35 c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;

- d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- 10 i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
110. The method, use, or pharmaceutical composition for use according to any of claims 92 to 109, wherein the asthma is moderate to severe asthma.
- 15 111. The method, use, or pharmaceutical composition for use according to any of claims 92 to 110, wherein the pharmaceutical composition is delivered by dry powder inhaler.
112. The method, use, or composition for use according to any of claims 110 to 111, wherein the asthma is uncontrolled moderate to severe asthma.
113. The method, use, or composition for use according to any of claims 92 to 112, wherein the
- 20 subject has a history of ≥ 1 severe exacerbation within the last 12 months prior to the treatment.
114. The method, use, or composition for use according to any of claims 92 to 113, wherein the subject has a history of ≥ 2 severe exacerbations within the last 12 months prior to the treatment.
115. The method, use, or composition for use according to any of claims 92 to 114, wherein the subject is co-administered a background therapy.
- 25 116. The method, use, or composition for use according to claim 115, wherein the subject is already receiving the background therapy prior to the treatment.
117. The method, use, or composition for use according claim 115 or 116, wherein the background therapy is selected from: inhaled corticosteroids, Leukotriene modifiers, long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), combination therapies such
- 30 as Fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol and fluticasone and vilanterol, theophylline, short-acting beta agonists (SABAs), ipratropium or a combination of ipratropium and albuterol or oral corticosteroids.
118. The method, use, or composition for use according to any of claims 115 to 117, wherein the background therapy comprises medium or high dose ICS (as per GINA 2023 report) in combination with LABA (GINA step 4 or 5 therapy).
- 35 119. The method, use, or composition for use according to any of claims 92 to 118, wherein the subject has a baseline blood eosinophil count of ≥ 150 cells/ μ l.

120. The method, use, or composition for use according to any of claims 92 to 118, wherein the subject has a baseline blood eosinophil count of ≥ 300 cells/ μ l.
121. The method, use, or composition for use according to claim 119 or 120, wherein baseline refers to the blood eosinophil count prior to commencement of the treatment.
- 5 122. The method, use, or composition for use according to claim 121, wherein prior means within one month of the commencement of the treatment.
123. A unit dose pharmaceutical composition comprising from 0.2 milligrams to 16 milligrams of an antigen binding fragment of an anti-TSLP antibody, wherein the pharmaceutical composition and antigen binding fragment are as described herein.
- 10 124. A method of treating COPD in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody, wherein the pharmaceutical composition is administered once daily (Q1D) by inhalation.
- 15 125. A pharmaceutical composition for use in a method of treating COPD in a subject in need thereof, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody that is to be administered to the subject one daily (Q1D) by inhalation.
- 20 126. Use of an antigen binding fragment of an anti-TSLP-antibody in the manufacture of a pharmaceutical composition for the treatment of COPD by inhalation, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of the antigen binding fragment.
- 25 127. A method of treating COPD in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody, wherein the pharmaceutical composition is administered once daily (Q1D) by inhalation and wherein the antigen binding fragment is a Fab comprising:
- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
 - d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
 - 30 e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
 - f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.
- 35 128. A pharmaceutical composition for use in a method of treating COPD in a subject in need thereof, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of an antigen binding fragment of an anti-TSLP-antibody that is to be administered to the subject once daily (Q1D) by inhalation, wherein the antigen binding fragment is a Fab comprising:
- a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
 - b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
 - c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;

- d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
- e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
- f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7.

5 129. Use of an antigen binding fragment of an anti-TSLP-antibody in the manufacture of a pharmaceutical composition for the treatment of COPD, wherein the pharmaceutical composition comprises a dose of about 0.4 mg to about 8 mg of the antigen binding fragment, wherein the antigen binding fragment is a Fab comprising:

- 10 a. a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1;
- b. a HCDR2 comprising the amino acid sequence of SEQ ID NO: 2;
- c. a HCDR3 comprising the amino acid sequence of SEQ ID NO: 3;
- d. a LCDR1 comprising the amino acid sequence of SEQ ID NO: 5;
- e. a LCDR2 comprising the amino acid sequence of SEQ ID NO: 6; and
- f. a LCDR3 comprising the amino acid sequence of SEQ ID NO: 7,

15 and the pharmaceutical composition is to be administered once daily (Q1D) by inhalation.

130. The method, use, or pharmaceutical composition for use according to any of claims 124 to 129, wherein the antigen binding fragment comprises a VH domain having a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 4 and a VL domain having a sequence at least 95%, 90%, 85% or 80% identical to SEQ ID NO: 8.

20 131. The method, use, or pharmaceutical composition for use according to any of claims 124 to 130, wherein the antigen binding fragment comprises a VH domain comprising the sequence of SEQ ID NO: 4; and a VL domain comprising the sequence of SEQ ID NO: 8.

132. The method, use, or pharmaceutical composition for use according to any of claims 124 to 131, wherein the Fab is of an IgG1 antibody.

25 133. The method, use, or pharmaceutical composition for use according to claim 132, wherein the antigen binding fragment comprises a first sub-unit having the sequence set forth in SEQ ID NO: 28 and a second sub-unit having the sequence set forth in SEQ ID NO: 29.

30 134. The method, use, or pharmaceutical composition for use according to any of claims 124 to 133, wherein the pharmaceutical composition comprises spray-dried particles comprising:

- a. about 5% (w/w) to about 15% (w/w) leucine;
- b. about 1% (w/w) to about 5% (w/w) trileucine;
- c. about 1% (w/w) to about 50% (w/w) of an antigen binding fragment of an anti-thymic stromal lymphopoietin (TSLP) antibody;
- 35 d. a buffer; and
- e. a glass stabilisation agent.

40 135. The method, use, or pharmaceutical composition for use according to claim 134, comprising about 1% (w/w) to about 10% (w/w) histidine buffer at a pH of between about pH 5 to pH 6.

136. The method, use, or pharmaceutical composition for use according to claims 134 or 135, comprising about 1% (w/w) to about 3% (w/w) trileucine.
137. The method, use, or pharmaceutical composition for use according to claim 136, comprising about 2% (w/w) trileucine.
- 5 138. The method, use, or pharmaceutical composition for use according to any of claims 134 to 137, comprising about 8% (w/w) to about 12% (w/w) leucine.
139. The method, use, or pharmaceutical composition for use according to claim 138, comprising about 10.5% (w/w) leucine.
- 10 140. The method, use, or pharmaceutical composition for use according to any of claims 134 to 139, comprising about 1% (w/w) to about 5% (w/w) histidine buffer.
141. The method, use, or pharmaceutical composition for use according to claim 140, comprising about 2.5% (w/w) to about 3.5% (w/w) histidine buffer.
142. The method, use, or pharmaceutical composition for use according to claim 141, comprising about 3.14% (w/w) histidine buffer.
- 15 143. The method, use, or pharmaceutical composition for use according to any of claims 134 to 142, wherein the antigen binding fragment is present at a concentration of about 2% (w/w), about 10% (w/w) or about 40% (w/w).
144. The method, use, or pharmaceutical composition for use according to any of claims 134 to 143, wherein the antigen binding fragment is present at a concentration of about 2% (w/w).
- 20 145. The method, use, or pharmaceutical composition for use according to any of claims 134 to 143, wherein the antigen binding fragment is present at a concentration of about 10% (w/w).
146. The method, use, or pharmaceutical composition for use according to any of claims 134 to 143, wherein the antigen binding fragment is present at a concentration of about 40% (w/w).
- 25 147. The method, use, or pharmaceutical composition for use according to any of claims 134 to 146, wherein the glass stabilization agent is selected from trehalose, sucrose, raffinose, inulin, dextran, mannitol, and cyclodextrin.
148. The method, use, or pharmaceutical composition for use according to claim 147, wherein the glass stabilization agent is trehalose.
- 30 149. The method, use, or pharmaceutical composition for use according claim 148, wherein the trehalose is at a percent (w/w) concentration to make up to about 100%.
150. The method, use, or pharmaceutical composition for use according to any of claims 134 to 149, wherein the composition does not comprise a surfactant.
151. The method, use, or pharmaceutical composition for use according to any of claims 134 to 150, comprising:
- 35 a. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 84.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;

- b. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 82.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- c. 2% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 80.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 5 d. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 76.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5;
- e. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 74.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- 10 f. 10% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 72.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5;
- g. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 44.36% (w/w) trehalose $\pm$ 10%, and 3.14% (w/w) histidine $\pm$ 10%, at pH 5.5;
- h. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 42.5% (w/w) trehalose $\pm$ 10%, and 5.0% (w/w) histidine $\pm$ 10%, at pH 5.5; or
- 15 i. 40% (w/w) antigen binding fragment $\pm$ 20%, 2% (w/w) trileucine $\pm$ 10%, 10.5% (w/w) leucine $\pm$ 10%, 46.2% (w/w) trehalose $\pm$ 10%, and 1.3% (w/w) histidine $\pm$ 10%, at pH 5.5.
152. The method, use, or pharmaceutical composition for use according to any of claims 134 to 151, wherein the pharmaceutical composition is delivered by dry powder inhaler.
153. The method, use, or composition for use according to any of claims 134 to 152, wherein
20 the subject has a history of $\geq$ 1 severe exacerbation within the last 12 months prior to the treatment.
154. The method, use, or composition for use according to any of claims 134 to 153, wherein the subject has a history of $\geq$ 2 severe exacerbations within the last 12 months prior to the treatment.
155. The method, use, or composition for use according to any of claims 134 to 154, wherein
25 the subject is co-administered a background therapy.
156. The method, use, or composition for use according to claim 155, wherein the subject is already receiving the background therapy prior to the treatment.
157. The method, use, or composition for use according claim 155 or 156, wherein the
30 background therapy is selected from: inhaled corticosteroids, Leukotriene modifiers, long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), combination therapies such as Fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol and fluticasone and vilanterol, theophylline, short-acting beta agonists (SABAs), ipratropium or a combination of ipratropium and albuterol or oral corticosteroids.
158. The method, use, or composition for use according to any of claims 155 to 157, wherein
35 the background therapy comprises medium or high dose ICS (as per GINA 2023 report) in combination with LABA (GINA step 4 or 5 therapy).
159. The method, use, or composition for use according to any of claims 134 to 158, wherein the subject has a baseline blood eosinophil count of $\geq$ 150 cells/ μ l.

160. The method, use, or composition for use according to any of claims 134 to 158, wherein the subject has a baseline blood eosinophil count of ≥ 300 cells/ μ l.
161. The method, use, or composition for use according to claim 159 or 160, wherein baseline refers to the blood eosinophil count prior to commencement of the treatment.
- 5 162. The method, use, or composition for use according to claim 161, wherein prior means within one month of the commencement of the treatment.