

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

SUMMARY

In one aspect of the present disclosure, there is provided a pharmaceutical formulation comprising:

- (i) 50 mg/mL – 150 mg/mL of an IL-23p19 antibody;
 - (ii) 8 mM – 12 mM of a citrate buffer;
 - (iii) 100 - 200 mM of sodium chloride (NaCl); and
 - (iv) 0.01% w/v to 0.05% w/v of a surfactant,
- wherein the pH of the formulation is about 5.5, and
- wherein the anti-IL-23p19 antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.

In another aspect of the present disclosure, there is provided a pharmaceutical formulation comprising:

- (i) 50 mg/mL – 150 mg/mL of an antibody IL-23p19 antibody;
 - (ii) 3mM - 12mM of a histidine buffer;
 - (iii) 25 - 75 mM of NaCl;
 - (iv) 2-5% w/v of a tonicity agent; and
 - (iv) 0.01% w/v to 0.05% w/v of a surfactant,
- wherein the pH of the formulation is between 5.0 to 6.0, and
- wherein the anti-IL-23p19 antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of the LCVR is SEQ ID NO: 8 and the amino acid sequence of the HCVR is SEQ ID NO: 7.

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

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

In a further aspect of the present disclosure, there is provided a pharmaceutical formulation disclosed herein for use in reducing injection-associated pain in a patient, wherein the pharmaceutical formulation is to be SC, IP and/or IM administered to the patient and the patient experiences reduced injection-associated pain at the time of, or shortly after, SC, IP and/or IM administration of the pharmaceutical formulation, and the pharmaceutical formulation provides a therapeutically favorable level of injection-associated pain.

In another aspect of the present disclosure, there is provided a pharmaceutical formulation disclosed herein for improved SC administration of an anti-IL-23p19 antibody to a patient in need thereof, wherein the pharmaceutical formulation is to be SC administered to the patient and the improvement comprises a reduction in injection-associated pain upon SC administration, an improved level of injection-associated pain and/or a therapeutically favorable level of injection-associated pain.

In a further aspect of the present disclosure, there is provided a pharmaceutical formulation disclosed herein for improved treatment of at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis, wherein the pharmaceutical formulation is to be SC administered to a patient and the improvement comprises a reduction in injection-associated pain upon SC administration, an improved level of injection-associated pain and/or a therapeutically favorable level of injection-associated pain.

In another aspect of the present disclosure, there is provided a pharmaceutical formulation disclosed herein for use in therapy.

DESCRIPTION

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

Accordingly, there is provided a pharmaceutical formulation comprising:

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

CLAIMS:

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

8. A pharmaceutical composition according to any preceding claim, wherein the concentration of the citrate buffer is about 10 mM.
9. A pharmaceutical formulation according to any preceding claim, wherein the citrate buffer is a sodium citrate buffer.
10. A pharmaceutical formulation according to any preceding claim, wherein the surfactant is polysorbate 20 or polysorbate 80.
11. A pharmaceutical formulation according to claim 10, wherein the surfactant is polysorbate 80.
12. A pharmaceutical formulation according to any one of claims 1-11, wherein the concentration of the surfactant is about 0.03% (w/v).
13. A pharmaceutical formulation according to any one of claims 1-12, wherein the concentration of NaCl is about 150 mM.

~~14. — A pharmaceutical formulation according to any one of claims 1-13, wherein the pH of the formulation is about 5.5.~~

~~14~~15. A pharmaceutical formulation according to claim 3, wherein the formulation comprises:

- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
- (ii) 10 mM of sodium citrate buffer;
- (iii) 150 mM of NaCl; and
- (iv) 0.03% w/v of polysorbate 80,

wherein the pH of the formulation is about 5.5.

~~15~~16. A pharmaceutical formulation according to claim ~~14~~15, wherein the formulation comprises 100 mg/mL of mirikizumab.

1617. A pharmaceutical formulation according to claim 1415, wherein the formulation comprises 125 mg/mL of mirikizumab.

1718. A pharmaceutical formulation comprising:

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

wherein the pH of the formulation is between 5.0 to 6.0, and

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

1819. A pharmaceutical formulation according to claim 1718, wherein the anti-IL-23p19 antibody comprises a light chain (LC) and a heavy chain (HC), wherein the amino acid sequence of the LC is SEQ ID NO: 10 and the amino acid sequence of the heavy chain is SEQ ID NO: 9.

1920. A pharmaceutical formulation according to claim 1718 or claim 1819, wherein the anti-IL-23p19 antibody is mirikizumab.

2021. A pharmaceutical formulation according to any one of claims 17-1918-20, wherein the concentration of the anti-IL-23p19 antibody is about 75 mg/mL to about 150 mg/mL.

2122. A pharmaceutical formulation according to any one of claims 17-2018-21, wherein the concentration of the anti-IL-23p19 antibody is about 100 mg/mL to about 150 mg/mL.

2223. A pharmaceutical formulation according to any one of claims 17-2118-22, wherein the concentration of the anti-IL-23p19 antibody is about 100 mg/mL.

2324. A pharmaceutical formulation according to any one of claims 17-21,~~18-22~~ wherein the concentration of the anti-IL-23p19 antibody is about 125 mg/mL.

2425. A pharmaceutical composition according to any one of claims 17~~18~~-23, wherein the concentration of the histidine buffer is about 5 mM.

2526. A pharmaceutical composition according to any one of claims 17-24~~18-25~~, wherein the tonicity agent is mannitol.

2627. A pharmaceutical composition according to claim 2526, wherein the concentration of mannitol is 3.3% w/v.

2728. A pharmaceutical formulation according to any one of claims 17-26~~18-27~~, wherein the surfactant is polysorbate 20 or polysorbate 80.

2829. A pharmaceutical formulation according to claim 2728, wherein the surfactant is polysorbate 80.

2930. A pharmaceutical formulation according to any one of claims 17-28~~18-29~~, wherein the concentration of the surfactant is about 0.03% (w/v).

3031. A pharmaceutical formulation according to any one of claims 17-29~~18-30~~, wherein the concentration of NaCl is about 50 mM.

3132. A pharmaceutical formulation according to any one of claims 17-30~~18-31~~, wherein the pH of the formulation is about 5.5.

3233. A pharmaceutical formulation according to claim 19~~20~~ comprising:

- (i) 100 mg/mL or 125 mg/mL of mirikizumab;
- (ii) 5 mM of a histidine buffer;
- (iii) 50 mM of NaCl;

- (iv) 3.3% w/v of mannitol; and
- (v) 0.03% w/v of polysorbate 80,

wherein the pH of the formulation is 5.5.

3334. A pharmaceutical formulation according to claim 32, wherein the formulation comprises 100 mg/mL of mirikizumab.

3435. A pharmaceutical formulation according to claim 32, wherein the formulation comprises 125 mg/mL of mirikizumab.

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

3537. A pharmaceutical formulation according to any one of claims 1-~~3435~~ for use in the treatment and/or prevention of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

3638. Use of a pharmaceutical formulation according to any one of claims 1-~~3435~~ in the manufacture of a medicament for ~~use in~~ the treatment of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and/or ankylosing spondylitis.

3739. A pharmaceutical formulation according to any one of claims 17-36 for use in~~A method of~~ reducing injection-associated pain in a patient, wherein the pharmaceutical formulation is to be SC, IP and/or IM administered to the patient and the ~~experienced by a patient~~ experiences reduced injection-associated pain at the time of, or shortly after, SC, IP and/or IM administration of thea pharmaceutical formulation, and the pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering to a patient a pharmaceutical formulation according to any one of claims 18-35, wherein, said step of administering provides a therapeutically favorable level of injection-associated pain.

3840. The pharmaceutical formulation for use according to claim 37, ~~A method of reducing injection-associated pain according to claim 39,~~ wherein the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

3941. A pharmaceutical formulation according to any one of claims 17-36 for ~~An improved method for~~ SC administration of an anti-IL-23p19 antibody to a patient in need thereof, wherein the pharmaceutical formulation is to be SC administered to the patient and the improvement comprises a reduction in injection-associated pain upon SC administration, ~~of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical formulation according to of any of claims 18-35, wherein said step of administering provides~~ an improved level of injection-associated pain and/or ~~provides~~ a therapeutically favorable level of injection-associated pain.

4042. ~~The pharmaceutical formulation An improved method for SC administration of an anti-IL-23p19 antibody~~ according to claim 3941, wherein the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

4143. A pharmaceutical formulation according to any one of claims 17-36 for improved treatment of ~~An improved method of treating~~ at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis, wherein the pharmaceutical formulation is to be SC administered to a patient and the improvement comprises a reduction in injection-associated pain upon ~~the SC administration of a pharmaceutical formulation comprising an anti-IL-23p19 antibody, the method comprising administering a pharmaceutical formulation according to any one of claims 18-35, wherein said step of administering provides,~~ an improved level of injection-associated pain and/or ~~provides~~ a therapeutically favorable level of injection-associated pain.

4244. The pharmaceutical formulation~~An improved method of treating at least one of psoriasis, ulcerative colitis, Crohn's Disease, psoriatic arthritis and ankylosing spondylitis~~ according to claim 4143, wherein the therapeutically favorable level of injection-associated pain comprises a VAS score of less than 30 mm or less than 20 mm.

43. The pharmaceutical formulation according to any one of claims 17-36 for use in therapy.