SUMMARY

[0011] The compositions of the ~~invention~~ disclosure are based, at least in part, on the discovery that anti-IL13 antibody described herein, lebrikizumab, can be formulated at high concentration (> 100 mg/mL) in a histidine buffer containing polyol and surfactant and that such high antibody concentration formulation is of low viscosity, has extended physical and chemical stability and maintains potency. Compositions or formulations of the ~~invention~~ disclosure are useful for, e.g., the treatment of asthma and other lung disorders such as idiopathic pulmonary fibrosis and certain allergic, autoimmune and other inflammatory disorders. In addition, such formulation can be packaged into subcutaneous administration devices as described herein with maintenance of, for example, product stability and other desirable attributes.

[0012] Accordingly, ~~in one aspect,~~disclosed is a formulation comprising an anti-IL13 antibody ~~is provided~~. In certain embodiments, the concentration of antibody in the formulation is at least 100 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C.

[0012a] Hence, in one aspect, there is provided a formulation comprising an anti-IL13 antibody, wherein the concentration of antibody in the formulation is at least 100 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C. In ~~another~~ one embodiment, the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7. In one embodiment, the anti-IL13 antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10. In one embodiment, the anti-IL13 antibody comprises a light chain having the amino acid sequence of SEQ ID NO.: 14. In one embodiment, the anti-IL13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14. In one embodiment, the concentration of antibody is 125 mg/mL. In one embodiment, the concentration of antibody is 150 mg/mL.

[0013] In another ~~aspect~~embodiment, the formulation comprises histidine acetate buffer, ph 5.4 to 6.0, and the histidine acetate concentration in the buffer is between 5 mM and 40 mM. In certain

embodiments, the formulation comprises a polyol and a surfactant and the concentration of the polyol in the formulation is between 100 mM and 200 mM and the concentration of the surfactant in the formulation is between 0.01% and 0.1%. In certain embodiments, the polyol is sucrose and the surfactant is polysorbate 20. In certain embodiments, the histidine acetate buffer is pH 5.7 and the histidine acetate concentration in the buffer is 20mM, and the concentration of sucrose in the formulation is 175 mM and the concentration of polysorbate 20 is 0.03%. In one embodiment, the concentration of antibody is 125 mg/mL or 150 mg/mL. In one embodiment, the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6.

[0014] In ~~yet~~ another aspect, there is provided a formulation ~~comprises~~ comprising an anti-IL13 antibody in a histidine acetate buffer, pH 5.4 to 6.0, ~~and~~ wherein the histidine acetate concentration in the buffer is between 5 mM and 40 mM and wherein the concentration of antibody in the formulation is at least 100 mg/mL. In certain embodiments, the formulation further comprises a polyol and a surfactant, and the concentration of the polyol in the formulation is between 100 mM and 200 mM and the concentration of the surfactant in the formulation is between 0.01% and 0.1%. In one embodiment, the polyol is sucrose and the surfactant is polysorbate 20. In one embodiment, the histidine acetate buffer is pH 5.7 and the histidine acetate concentration in the buffer is 20mM, and wherein the concentration of sucrose in the formulation is 175 mM and the concentration of polysorbate 20 is 0.03%. In one embodiment, the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7. In one embodiment, the anti-IL13 antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL13 antibody comprises a heavy chain having the amino acid sequence

of SEQ ID NO.: 10. In one embodiment, the anti-IL13 antibody comprises a light chain having the amino acid sequence of SEQ ID NO.: 14. In one embodiment, the anti-IL13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14. In one embodiment, the formulation has a viscosity of less than 15 centipoise (cP) at 25°C. In one embodiment, the concentration of antibody is 125 mg/mL. In one embodiment, the concentration of antibody is 150 mg/mL.

[0015] ~~In still another aspect,~~Also disclosed is a formulation comprising an antiIL-13 antibody having extended stability~~ is provided~~. In certain embodiments, the antibody concentration is at least 100 mg/mL and the viscosity is less than 15 centipoise (cP) at 25°C.

[0015a] Hence, in one embodiment, there is provided a formulation comprising an antiIL-13 antibody having extended stability, wherein the antibody concentration is at least 100 mg/mL and the viscosity is less than 15 centipoise (cP) at 25°C. In one embodiment, the antiIL-13 antibody is stable for at least one year at 5°C. In one embodiment, the antiIL-13 antibody is stable for at least two years at 5°C. In one embodiment, the anti-IL13 antibody is stable for three years at 5°C. In one embodiment, the anti-IL13 antibody is stable for at least four weeks at 25°C, or at least 8 weeks at 25°C, or at least 12 weeks at 25°C, or for 26 weeks at 4°C. In one embodiment, the formulation comprises histidine acetate buffer, ph 5.4 to 6.0, and the histidine acetate concentration in the buffer is between 5 mM and 40 mM. In one embodiment, the formulation further comprises a polyol and a surfactant, and the concentration of the polyol in the formulation is between 100 mM and 200 mM and the concentration of the surfactant in the formulation is between 0.01% and 0.1%. In one embodiment, the polyol is sucrose and the surfactant is polysorbate 20. In one embodiment, the histidine acetate buffer is pH 5.7 and the histidine acetate concentration in the buffer is 20mM, and the concentration of sucrose in the formulation is 175 mM and the concentration of polysorbate 20 is 0.03%. In one embodiment, the concentration of antibody is 125 mg/mL or 150 mg/mL. In one embodiment, the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6.

[0016] ~~In yet another aspect,~~Also disclosed is a formulation comprising an anti-IL13 antibody having extended stability in 20 mM histidine acetate buffer, pH 5.7, 175 mM sucrose, 0.03% polysorbate 20~~ is provided~~. In one embodiment, the concentration of antibody in the formulation is 125 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C. In one embodiment, the concentration of antibody in the formulation is 150 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C. In one embodiment, the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6.

[0016a] Hence, in one aspect, there is provided a formulation comprising an anti-IL13 antibody having extended stability in 20 mM histidine acetate buffer, pH 5.7, 175 mM sucrose, 0.03% polysorbate 20, wherein the concentration of antibody in the formulation is 125 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C, and wherein the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In another aspect, there is provided a formulation comprising an anti-IL13 antibody having extended stability in 20 mM histidine acetate buffer, pH 5.7, 175 mM sucrose, 0.03% polysorbate 20, wherein the concentration of antibody in the formulation is 150 mg/mL and the viscosity of the formulation is less than 15 centipoise (cP) at 25°C, and wherein the anti-IL13 antibody comprises three heavy chain CDRs, CDR-H1 having the amino acid sequence of SEQ ID NO.: 1, CDR-H2 having the amino acid sequence of SEQ ID NO.: 2, and CDR-H3 having the amino acid sequence of SEQ ID NO.: 3, and three light chain CDRs, CDR-L1 having the amino acid sequence of SEQ ID NO.: 4, CDR-L2 having the amino acid sequence of SEQ ID NO.: 5, and CDR-L3 having the amino acid sequence of SEQ ID NO.: 6. In one embodiment, the anti-IL13 antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO.: 7 and a light chain variable region having the amino acid sequence of SEQ ID NO.: 9. In one embodiment, the anti-IL13 antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO.: 10 and a light chain having the amino acid sequence of SEQ ID NO.: 14.

[0017] ~~In still a further aspect,~~Further disclosed is an article of manufacture comprising a subcutaneous administration device ~~is provided~~. In one aspect, there is provided an article of manufacture comprising the formulation as defined above and a subcutaneous administration device. In certain embodiments, the subcutaneous administration device delivers to a patient a flat dose of an anti-IL13 antibody. In one embodiment, the flat dose is 37.5 mg of anti-IL13 antibody. In one embodiment, the flat dose is 75 mg of anti-IL13 antibody. In one embodiment, the flat dose is 125 mg of anti-IL13 antibody. In one embodiment the flat dose is 150 mg of anti-IL13 antibody. In certain embodiments, the anti-IL13 antibody is lebrikizumab. The anti-IL 13 antibody in the subcutaneous administration device is formulated in a buffer and other excipients as described above such that it is provided in a stable pharmaceutical formulation. In certain embodiments, the subcutaneous administration device is a prefilled syringe comprising a glass barrel, a plunger rod comprising a plunger stopper and a needle. In certain embodiments, the subcutaneous administration device further comprises a needle shield and optionally a needle shield device. In certain embodiments, the volume of formulation contained in the prefilled syringe is 0.3 mL, 1 mL, 1.5 mL, or 2.0 mL. In certain embodiments, the needle is a staked-in needle comprising a 3-bevel tip or a 5-bevel tip. In certain embodiments, the needle is between 25 gauge (G) and 30G and is between 1/2 inch long and 5/8 inch long. In one embodiment, the

subcutaneous administration device comprises a prefilled 1.0 mL low tungsten borosilicate glass (type I) syringe and a stainless steel 5-bevel 27G 1/2 inch long thin-wall staked-in needle. In certain embodiments, the subcutaneous administration device comprises a rigid needle shield. In certain embodiments, the rigid needle shield comprises a rubber formulation having low zinc content. In one embodiment, the needle shield is rigid and comprises an elastomeric component, FM27/0, and rigid polypropylene shield. In certain embodiments, the plunger rod comprises a rubber plunger stopper. In certain embodiments, the rubber plunger stopper comprises 4023/50 rubber and FluroTec® ethylene-tetrafluoroethylene (ETFE) coating. In certain embodiments, the subcutaneous administration device comprises a needle safety device. Exemplary needle safety devices include, but are not limited to, Ultrasafe Passive® Needle Guard X100L (Safety Syringes, Inc.) and Rexam Safe n Sound™ (Rexam).

[0017a] In one aspect, there is provided use of an effective amount of the formulation as defined above in the manufacture of a medicament for treating asthma in a patient.

[0017b] In one aspect, there is provided use of an effective amount of the formulation as defined above in the manufacture of a medicament for treating idiopathic pulmonary fibrosis in a patient.

[0017c] In one aspect, there is provided use of an anti-IL13 antibody in the manufacture of a formulation for subcutaneous administration, wherein the subcutaneous administration comprises the subcutaneous administration device as defined above.

[0018] ~~In yet another aspect,~~Also disclosed is a method of treating asthma in a patient ~~is provided~~. In certain embodiments, the method comprises administering to the patient an effective amount of any of the above formulations. In certain embodiments, the effective amount is 0.3 mL, one-half mL, one mL or two mL, or about 0.3 mL, about one-half mL, about one mL or about two mL. ~~In another aspect,~~Further disclosed is a method of treating idiopathic pulmonary fibrosis in a patient ~~is provided~~. In certain embodiments, the method comprises administering to the patient an effective amount of any of the above formulations. In certain embodiments, the effective amount is one-half mL, one mL or two mL, or about one-half mL, about one mL or about two mL.

[0019] ~~In still yet another aspect,~~Yet further disclosed are methods of administering subcutaneously a formulation comprising and anti-IL13 antibody ~~are provided~~. Such methods comprise administering subcutaneously any of the anti-IL13 antibody formulations described above. In certain embodiments, the methods comprise a subcutaneous administration device according to any of the devices described above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] Figure 1 shows the rate of anti-IL13 antibody monomer degradation per week as a function of pH as described in Example 1.

[0021] Figure 2 shows increases in solution turbidity at 350 nm of anti-IL13 antibody solutions as a function of pH during storage at 30°C as described in Example 1.

55. The article of manufacture of claim 54 further comprising a plunger rod and a plunger stopper.
56. The article of manufacture of claim 55 further comprising a needle safety device.
57. The article of manufacture of any one of claims 54-56 wherein the glass barrel comprises borosilicate glass and contains about 0.3 mL, about 1.0 mL, or about 2.0 mL of the formulation.
58. The article of manufacture of any one of claims 55-57 wherein the plunger stopper comprises 4023/50 rubber and ethylene-tetrafluoroethylene coating.
59. The article of manufacture of any one of claims 54-58 wherein the needle is staked-in, stainless steel, 27G thin-wall, 1/2 inch long, and 5-bevel tip.
60. The article of manufacture of any one of claims 54-59 wherein the needle shield is rigid and comprises an elastomeric component, FM27/0, and rigid polypropylene shield.
61. ~~A method of treating asthma in a patient comprising administering to the patient~~Use of an effective amount of the formulation of any one of claims 1-51 in the manufacture of a medicament for treating asthma in a patient.
62. The ~~method~~ use of claim 61 wherein the effective amount is 0.3 mL, one mL or two mL or about 0.3 mL, about one mL or about two mL.
63. ~~A method of treating idiopathic pulmonary fibrosis in a patient comprising administering to the patient~~Use of an effective amount of the formulation of any one of claims 1-51 in the manufacture of a medicament for treating idiopathic pulmonary fibrosis in a patient.
64. The ~~method~~ use of claim 62 wherein the effective amount is 0.3 mL, one mL or two mL or about 0.3 mL, about one mL or about two mL.
65. ~~A method of administering subcutaneously a formulation comprising~~Use of an anti-IL13 antibody in the manufacture of a formulation for subcutaneous administration, ~~the method comprising~~wherein the subcutaneous administration comprises the subcutaneous administration device of any one of claims 52-60.
66. The ~~method~~ use of claim 65 comprising the formulation of any one of claims 1-51.