CLAIMS

1. A liquid aqueous formulation comprising:

(1) an isolated human anti-TNFα antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8~~, or an antigen-binding portion thereof~~;

(2) a polysorbate~~surfactant~~; and,

(3) less than 50 mg/ml of mannitol or sorbitol~~a polyol~~;

wherein the formulation has a pH of 4.7 to 5.7 and does not contain a buffer or a salt, and wherein injection of the formulation into a human subject results in a Pain Visual Analog Scale (VAS) score of less than 1.0.

2. A liquid aqueous formulation comprising:

(1) an isolated human anti-TNFα antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8~~, or an antigen-binding portion thereof~~;

(2) a polysorbate~~surfactant~~; and,

(3) less than 50 mg/ml of mannitol or sorbitol~~a polyol~~;

wherein the formulation has a pH of 4.7 to 5.7 and ~~wherein the formulation~~ does not contain a buffer or a salt, and

wherein injection of the formulation reduces pain associated with the injection in a human subject by at least about 50% when compared to injection of an otherwise identical formulation that comprises a salt and/or a buffer.

3. A liquid aqueous formulation consisting essentially of:

(1) more than 50 mg/ml of an isolated human anti-TNFα antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6~~or antigen-binding portion thereof~~;

(2) a olysorbate~~surfactant~~; and

(3) less than 50 mg/ml of mannitiol or sorbitol~~a polyol~~,

wherein the formulation has a pH of 4.7 to 5.7, and wherein injection of the formulation into a human subject results in a Pain Visual Analog Scale (VAS) score of less than 1.0.

4. The formulation of claim 2, wherein the pain associated with the injection is assessed using a Pain Visual Analog Scale (VAS).

5. The formulation of claim 2, wherein the otherwise identical formulation comprises a citrate phosphate buffer and sodium chloride.

6. A liquid aqueous formulation comprising:

(1) an isolated human anti-TNFα antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO:~~, or an antigen-binding portion thereof~~;

(2) a polysorbate~~surfactant~~; and,

(3) less than 50 mg/ml of mannitol or sorbitol ~~a polyol~~;

wherein the formulation has a pH of 4.7 to 5.7 and does not contain a buffer or a salt, and wherein the formulation is stable up to about 30°C for at least 6 days.

7. The formulation of claim 6, wherein the formulation is stable up to about 30°C for 10 days.

8. The formulation of claim 6, wherein the formulation is stable up to about 30°C for 14 days.

~~9. The formulation of any one of claims 1-8, wherein the polyol is mannitol or sorbitol.~~

9~~10~~. The formulation of any one of claims 1-8~~claim 9~~, comprising about 38-46 mg/ml of mannitol.

~~11. The formulation of any one of claims 1-10, wherein the surfactant is a polysorbate.~~

10~~12~~. The formulation of any one of claims 1-8 and 9~~claimclaim 11~~, wherein the polysorbate is polysorbate 80.

11~~13~~. The formulation of any one of claims 1-8 and 9~~claim 11~~, wherein the concentration of polysorbate is about 0.1 to 1.5.

12~~14~~. The formulation of any one of claims 1-8, 9, and 11~~claims 1-13~~, wherein the concentration of the anti-TNFα antibody, ~~or antigen-binding portion thereof,~~ is 95-105 mg/ml.

~~15. The formulation of any one of claims 1-14, wherein the antibody, or antigen binding portion thereof, dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance.~~

~~16. The formulation of any one of claims 1-14, wherein the antibody, or antigen binding portion thereof, has the following characteristics:~~

~~(1) dissociates from human TNFα with a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance;~~

~~(2) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine~~

~~substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; and~~

~~(3) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.~~

~~17. The formulation of any one of claims 1-14, wherein the antibody, or antigen binding portion thereof, has a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and has a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9,10 or 11, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.~~

13~~18~~. The formulation of any one of claims 1-12~~14~~, wherein the antibody, ~~or antigen binding portion thereof,~~ has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

14~~19~~. The formulation of any one of claims 1-12~~14~~, wherein the antibody is adalimumab or golimumab, or a biosimilar thereof.

15~~20~~. A liquid aqueous formulation consisting essentially of

(1) a concentration of 90-110 mg/ml of an isolated human anti-TNFα antibody~~, or an antigen-binding portion thereof,~~ having a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, ~~or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8,~~ a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1

domain comprising the amino acid sequence of SEQ ID NO: 7; and having a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, ~~or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9,10 or 11,~~ a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8;

(2) a polysorbate; and,

(3) about 38-46 mg/ml of mannitol, wherein the formulation has a pH of 4.7 to 5.7.

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16~~21~~. The formulation of any one of claims 1-8, 9, 10-12, 13, 14, and 15~~1-20~~, comprising about 30-90 mg of the antibody~~, or antigen binding portion thereof~~.

17~~22~~. A liquid aqueous formulation comprising:

(1) an isolated human anti-TNFα antibody comprising a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and comprises a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6~~, or an antigen-binding portion thereof~~;

(2) polysorbate-80~~a surfactant~~; and,

(3) less than 50 mg/ml of a mannitol~~polyol~~;

wherein the formulation has a pH of 4.7 to 5.7 and does not contain a buffer or a salt, and wherein the formulation has a characteristic selected from the group consisting of:

a) a conductivity of less than about 2 mS/cm;

b) a hydrodynamic diameter (D_h) which is at least about 50% less than the D_h of the protein in a buffered solution at a given concentration; and

c) a hydrodynamic diameter (D_h) of less than about 4 nm.

~~23. A pre-filled syringe or autoinjector device, comprising the formulation of any one of claims 1-22.~~

18~~24~~. Use of the formulation of any one of claims 1-17~~22~~ in the manufacture of a medicament for the treatment of a disorder associated with detrimental TNFα activity in a patient, wherein said medicament is to be administered to the patient.

1925. The use of claim 1824, wherein the disorder is selected from the group consisting of rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, juvenile

idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and hidradenitis suppurativa.

2026. The use of claim 1824, wherein the formulation is administered to the patient according to a periodicity selected from the group consisting of weekly, biweekly, every three weeks, and monthly.

2127. The use of claim 2026 wherein the administration is self-administration.

2228. Use of a formulation comprising an isolated human anti-TNFα antibody, or an antigen-binding portion thereof, in the manufacture of a medicament to be subcutaneously administered to a patient, such that injection pain is reduced upon administration,

wherein the formulation comprises more than 50 mg/ml of adalimumabthe antibody,

or antigen-binding portion thereof; polysorbate -80a surfactant; and less than 50 mg/ml of mannito,

wherein the formulation has a pH of 4.7 to 5.7 and does not contain a butter or a salta polyol.

2329. The use of claim 2228, wherein the injection pain is determined to be less than 1.0 according to a Pain Visual Analog Scale (VAS).

30. The use of claim 28 or 29, wherein the surfactant is a polysorbate.

2431. The use of claim 22 28 or 2329, wherein the concentration of polysorbate is about 0.1 to 1.5.

2532. The use of any one of claims 22-2428-31, wherein the formulation comprises more than 75 mg/ml of the antibody, or antigen-binding portion thereof.

33. The use of any one of claims 27-32, wherein the formulation comprises a polyol which is mannitol.

2634. The use of any one of claims 22-25claim 33, wherein the formulation comprises 38-46 mg/ml of mannitol.

35. Use of a formulation comprising a surfactant and an effective amount ofan isolated human anti-TNFα antibody, or an antigen-binding portion thereof, in the manufacture of a medicament to be administered to a human subject, such that the bioavailability of the antibody, or antigen-binding portion thereof, is improved, wherein the formulation does not contain a buffer, a polyol, or a salt.

36. Use of a formulation comprising a surfactant and an effective amount of an isolated human anti-TNFα antibody, or an antigen-binding portion thereof, in the

~~manufacture of a medicament to be administered to a human subject, such that the bioavailability of the antibody, or antigen-binding portion thereof, is improved, wherein the formulation has a characteristic selected from the group consisting of:~~

~~a) a conductivity of less than about 2 mS/cm;~~

~~b) the antibody, or antigen-binding portion thereof, has a hydrodynamic diameter (D_h) which is at least about 50% less than the D_h of the protein in a buffered solution at the given concentration; and~~

~~c) the antibody, or antigen-binding portion thereof, has a hydrodynamic diameter (D_h) of less than about 4 nm.~~

~~37. The use of claim 36, wherein the antibody, or antigen-binding portion thereof, has a hydrodynamic diameter (D_h) of less than about 2 nm.~~

~~38. The use of claim 36, wherein the conductivity of the formulation is less than about 1 mS/cm.~~

~~39. The use of any one of claims 35-38, wherein the effective amount of the antibody, or antigen-binding portion thereof, is 30-90 mg.~~

~~40. The use of any one of claims 35-38, wherein the concentration of the antibody, or antigen-binding portion thereof, in the pharmaceutical formulation is 90-110 mg/ml.~~

~~41. The use of any one of claims 35-38, wherein the bioavailability of the antibody, or antigen-binding portion thereof, is an AUC_{0-360} greater than 1300 μg * hr / ml when subcutaneously injected into the human subject.~~

~~42. The use of any one of claims 34-41, wherein the surfactant is a polysorbate.~~

~~43. The use of claim 42, wherein the surfactant is polysorbate 80.~~

~~44. The use of claim 43, wherein the concentration of polysorbate 80 is about 0.1 to 1.5.~~

~~45. Use of a formulation comprising a surfactant and an effective amount of an isolated human anti-TNFα antibody, or an antigen-binding portion thereof, in the manufacture of a medicament to be administered to a subject, such that the~~

~~bioavailability of the antibody, or antigen-binding portion thereof, in the subject is improved at least 15% over a second formulation,~~

~~wherein the formulation does not contain a buffer, a polyol, or a salt, and~~

~~wherein the second formulation comprises a buffer, a polyol, and a salt.~~

~~46. The use of claim 45, wherein the bioavailability of the antibody, or antigen-binding portion thereof, is improved at least 30% over the second formulation.~~

~~47. The use of claim 45, wherein the bioavailability of the antibody, or antigen-binding portion thereof, is improved at least 40% over the second formulation.~~

~~48. The use of claim 45, wherein the bioavailability is determined according to either an AUC level or a Cmax.~~

~~49. The use of claim 48, wherein the bioavailability is determined according to either an AUC_{0-360} or an AUC_{0-1344}.~~

~~50. The use of any one of claims 32-45, wherein the antibody, or antigen-binding portion thereof, is selected from the group consisting of~~

~~(1) an antibody, or antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance;~~

~~(2) an antibody, or antigen-binding portion thereof, having the following characteristics:~~

~~(a) dissociates from human TNFα with a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance;~~

~~(b) has a light chain CDR3 domain comprising the ammo acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; and~~

(c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12;

(3) an antibody, or antigen binding portion thereof, having a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7; and having a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9,10 or 11, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8;

(4) an antibody, or antigen binding portion thereof, having a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2; and

(5) adalimumab, or a biosimilar thereof; and

(6) golimumab, or a biosimilar thereof.

51. A liquid aqueous formulation consisting essentially of a surfactant and 30-90 mg of an isolated human anti-TNFα antibody, or an antigen-binding portion thereof,

wherein the formulation has an antibody concentration of 90-110 mg/ml, and

wherein the formulation provides increased bioavailability of the antibody, or antigen-binding portion thereof, to a human subject upon subcutaneous injection of the formulation relative to a formulation comprising a citrate phosphate buffer, sodium chloride, and mannitol.

52. A liquid aqueous formulation consisting essentially of a surfactant and 30-90 mg of an isolated human anti-TNFα antibody, or an antigen-binding portion,

wherein the formulation has an antibody concentration of 90-110 mg/ml, and

wherein the formulation provides increased bioavailability of the antibody, or antigen-binding portion thereof, in a human subject upon subcutaneous injection of the formulation, such that the antibody or antigen-binding portion thereof, has an AUC_{0-360} greater than 1300 μg * hr / ml.

53. The formulation of claim 51 or 52, wherein the antibody, or antigen-binding portion thereof, is selected from the group consisting of

(1) an antibody, or antigen binding portion thereof, that dissociates from human TNFα with a K_d of 1 x 10^{-8} M or less and has a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, both determined by surface plasmon resonance;

(2) an antibody, or antigen binding portion thereof, having the following characteristics:

(a) dissociates from human TNFα with a k_{off} rate constant of 1 x 10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

(b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9; and

(c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12;

(3) an antibody, or antigen binding portion thereof, having a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5, and a CDR1

~~domain comprising the amino acid sequence of SEQ ID NO: 7; and having a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9,10 or 11, a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6, and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8;~~

~~(4) an antibody, or antigen binding portion thereof, having a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2; and~~

~~(5) adalimumab, or a biosimilar thereof; and~~

~~(6) golimumab, or a biosimilar thereof.~~

~~54. The formulation of any one of claims 51-53, wherein the surfactant is polysorbate 80.~~

~~55. A pre-filled syringe or autoinjector device, comprising the formulation of any one of claims 53-54.~~

~~56. Use of the formulation of any one of claims 51-53 in the manufacture of a medicament for the treatment of a disorder associated with detrimental TNFα activity, wherein said medicament is to be administered to a patient.~~

~~57. The use of claim 56, wherein the disorder is selected from the group consisting of rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and hidradenitis suppurativa.~~

~~58. The use of claim 56, wherein the medicament is administered to the patient according to a periodicity selected from the group consisting of weekly, biweekly, every three weeks, and monthly.~~

~~59. The use of claim 58, wherein the administration is self-administration.~~