Claims

1. ~~A pharmaceutical formulation comprising: (i) an antibody that binds specifically to human delta-like ligand 4 (D114); (ii) a buffer at pH of 6.0 + 0.5; (iii) an organic cosolvent; and (iv) a two thermal stabilizers.~~ A pharmaceutical formulation consisting essentially of

(a) 25 mg/mL ± 3.75 mg/mL of an anti-Dll4 antibody;

(b) phosphate at a pH of 5.5 to 6.5;

(c) polysorbate 20;

(d) sodium chloride; and

(e) sucrose;

wherein the antibody is a human IgG1 antibody, comprises a heavy chain variable domain (HCVD) of SEQ ID NO: 1 and a light chain variable domain (LCVD) of SEQ ID NO: 5, and has a molecular weight of about 150 kDa; and wherein about 82% to about 87% of the antibodies are fucosylated.

~~2. The pharmaceutical formulation of claim 1, wherein the antibody comprises an HCDRl of SEQ ID NO: 2, an HCDR2 of SEQ ID NO: 3, an HCDR3 of SEQ ID NO: 4, an LCDR1 of SEQ ID NO: 6, an LCDR2 of SEQ ID NO: 7, and an LCDR3 of SEQ ID NO: 8.~~

~~3. The pharmaceutical formulation of claim 1 or claim 2, wherein the antibody comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5.~~

2. A pharmaceutical formulation comprising

(a) 25 mg/mL mL ± 3.75 mg/mL of an anti-D114 antibody,

(b) 10 mM ± 1.5 mM phosphate, pH 6 ± 0.3,

(c) 0.2% ± 0.03% polysorbate 20, (d) 150 mM ± 22.5 mM sodium chloride, and

(e) 10% ± 1.5% sucrose, wherein:

(a) the antibody is a human IgG1 antibody and comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5;

(b) the antibody a molecular weight of about 150 kDa; and

(c) about 82%) to about 87% of the antibodies are fucosylated.

3. The pharmaceutical formulation of claim 2 consisting of

(a) 25 mg/mL + 3.75 mg/mL of the antibody,

(b) 10 mM + 3 mM phosphate, pH 6 ± 0.5,

(c) 0.2% ± 0.03% polysorbate 20,

(d) 150 mM ± 22.5 mM sodium chloride, and

(e) 10% ± 1.5% sucrose, in water.

~~4. The pharmaceutical formulation of any one of claims 1-3, wherein~~

~~(a) the antibody has a molecular weight of about 150 kDa; and~~

~~(b) from about 82% to about 87% of the antibodies are fucosylated.~~

~~5. The pharmaceutical formulation of any one of claims 1-4, wherein the antibody concentration is 25 mg/mL ± 3.75 mg/mL.~~

~~6. The pharmaceutical formulation of any one of claims 1-5, wherein the buffer is phosphate.~~

~~7~~4. The pharmaceutical formulation of claim ~~6~~1, wherein the phosphate concentration is 10 mM ± 1.5 mM.

~~8. The pharmaceutical formulation of any one of claims 1-7, wherein the organic cosolvent is polysorbate 20.~~

~~9~~5. The pharmaceutical formulation of claim ~~8~~1, wherein the polysorbate 20 concentration is 0.2% w/v ± 0.03%.

~~10. The pharmaceutical formulation of any one of claims 1-9, wherein the stabilizer consists of sucrose and sodium chloride.~~

~~11~~6. The pharmaceutical formulation of claim ~~10~~1, wherein the sucrose concentration is 10% ± 1.5% (w/v) and the sodium chloride concentration is 150 mM ± 22.5 mM.

~~12~~7. The pharmaceutical formulation of ~~any one of~~ claim~~s~~ 1~~-11~~, comprising 25 mg/mL ± 3.75 mg/mL antibody, lOmM ± 1.5mM phosphate , pH 6 ± 0.5, 0.2% w/v + 0.03% polysorbate 20, 10% w/v ± 1.5% sucrose, and 150 mM ± 22.5 mM sodium chloride.

~~13~~8. The pharmaceutical formulation of any one of claims 1-~~12~~7, wherein at least 94% of the antibody has native conformation after 28 days of storage at 45°C.

~~14~~9. The pharmaceutical formulation of any one of claims 1-~~13~~8, wherein at least 45% of the antibody is the main charge form of the antibody after 28 days of storage at 45°C.

~~15~~10. The pharmaceutical formulation of any one of claims 1-~~14~~9, wherein at least 97% of the antibody has native conformation after 28 days of storage at 25°C.

~~16~~11. The pharmaceutical formulation of any one of claims 1-~~15~~10, wherein at least 57% of the antibody is the main charge form of the antibody after 28 days of storage at 25°C.

~~17~~12. The pharmaceutical formulation of any one of claims 1-~~16~~11, wherein at least 97% of the antibody has native conformation after 28 days of storage at 37°C.

~~18~~13. The pharmaceutical formulation of any one of claims 1-~~17~~12, wherein at least 51% of the antibody is the main charge form of the antibody after 28 days of storage at 37°C.

~~19~~14. The pharmaceutical formulation of any one of claims 1-~~18~~13, wherein at least 98% of the antibody has native conformation after six months of storage at 5°C.

~~20~~15. The pharmaceutical formulation of any one of claims 1-~~19~~14, wherein at least 61% of the antibody is the main charge form of the antibody after six months of storage at 5°C.

~~21~~16. The pharmaceutical formulation of any one of claims 1-~~20~~15, wherein the percent relative potency of the antibody after six months of storage at 5°C is ~~at least~~ 100% of the potency of the antibody prior to storage.

~~22~~17. The pharmaceutical formulation of any one of claims 1-~~21~~16, wherein at least

99% of the antibody has native conformation after six months of storage at -80°C.

~~23~~18. The pharmaceutical formulation of any one of claims 1-~~22~~17, wherein at least 57% of the antibody is the main charge form of the antibody after six months of storage at -80°C.

~~24~~19. The pharmaceutical formulation of any one of claims 1-~~23~~18, wherein the percent relative potency of the antibody after six months of storage at -80°C is ~~at least~~ 100% of the potency of the antibody prior to storage.

~~25~~20. The pharmaceutical formulation of any one of claims 1-~~24~~19, wherein at least 99% of the antibody has native conformation after six months of storage at -30°C.

~~26~~21. The pharmaceutical formulation of any one of claims 1-~~25~~20, wherein at least 57% of the antibody is the main charge variant of the antibody after six months of storage at -30°C.

~~27~~22. The pharmaceutical formulation of any one of claims 1-21~~-26~~, wherein the percent relative potency of the antibody after six months of storage at -30°C is at least 65% of the potency of the antibody prior to storage.

~~28~~23. The pharmaceutical formulation of any one of claims ~~1-27~~1-22, wherein at least 98% of the antibody has native conformation after six months of storage at -20°C.

~~29~~24. The pharmaceutical formulation of any one of claims ~~1-28~~1-23, wherein at least 60% of the antibody is the main charge variant of the antibody after six months of storage at -20°C.

~~30~~25. The pharmaceutical formulation of any one of claims ~~1-29~~1-24, wherein the percent relative potency of the antibody after six months of storage at -20°C is ~~at least~~ 100% of the potency of the antibody prior to storage.

~~31. A pharmaceutical formulation comprising (a) 25 mg/mL mL ± 3.75 mg/mL of an anti-D114 antibody, (b) 10 mM ± 1.5 mM phosphate, pH 6 ± 0.3, (c) 0.2% ± 0.03% polysorbate 20, (d) 150 mM ± 22.5 mM sodium chloride, and (d) 10% ± 1.5% sucrose, wherein:~~

~~(a) the antibody comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5;~~

~~(b) the antibody a molecular weight of about 150 kDa; and~~

~~(c) about 82%) to about 87% of the antibodies are fucosylated.~~

~~32. The pharmaceutical formulation of claim 31 consisting of (a) 25 mg/mL + 3.75 mg/mL of the antibody,~~

~~(b) 10 mM + 3 mM phosphate, pH 6 ± 0.5,~~

~~(c) 0.2% ± 0.03% polysorbate 20,~~

~~(d) 150 mM ± 22.5 mM sodium chloride, and~~

~~(e) 10% ± 1.5% sucrose, in water.~~

~~33~~26. A pharmaceutical composition of any one of claims ~~1-32~~1-25 ~~,~~ wherein said composition is contained in a container.

~~34~~27. The pharmaceutical composition of claim ~~33~~26, wherein the container is a vial.

~~35~~28. The pharmaceutical composition of claim ~~34~~27, wherein the vial is glass.

~~36~~29. The pharmaceutical composition of claim ~~33~~26, wherein the container is an IV drip bag.

~~37~~30. The pharmaceutical composition of claim ~~36~~29, wherein the bag is made of polyvinyl chloride.

~~38~~31. The pharmaceutical composition of claim ~~36~~29, wherein the bag is made of polyolefin.

~~39~~32. A kit comprising a pharmaceutical composition of any one of claims 1-25~~1-32~~, a container, and instructions.

~~40~~33. The kit of claim ~~39~~32, wherein the container is a glass vial fitted with ~~a FLUROTEC~~fluorocarbon-coated 4023/50 rubber stopper.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising: (i) an antibody that binds specifically to human delta-like ligand 4 (Dll4); (ii) a buffer at pH of 6.0 ± 0.5; (iii) an organic cosolvent; and (iv) a two thermal stabilizers.

2. The pharmaceutical formulation of claim 1, wherein the antibody comprises an HCDR1 of SEQ ID NO: 2, an HCDR2 of SEQ ID NO: 3, an HCDR3 of SEQ ID NO: 4, an LCDR1 of SEQ ID NO: 6, an LCDR2 of SEQ ID NO: 7, and an LCDR3 of SEQ ID NO: 8.

3. The pharmaceutical formulation of claim 1 or claim 2, wherein the antibody comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5.

4. The pharmaceutical formulation of any one of claims 1-3, wherein

(a) the antibody has a molecular weight of about 150 kDa; and

(b) from about 82% to about 87% of the antibodies are fucosylated.

5. The pharmaceutical formulation of any one of claims 1-4, wherein the antibody concentration is 25 mg/mL ± 3.75 mg/mL.

6. The pharmaceutical formulation of any one of claims 1-5, wherein the buffer is phosphate.

7. The pharmaceutical formulation of claim 6, wherein the phosphate concentration is 10 mM ± 1.5 mM.

8. The pharmaceutical formulation of any one of claims 1-7, wherein the organic cosolvent is polysorbate 20.

9. The pharmaceutical formulation of claim 8, wherein the polysorbate 20 concentration is 0.2% w/v ± 0.03%.

10. The pharmaceutical formulation of any one of claims 1-9, wherein the stabilizer consists of sucrose and sodium chloride.

11. The pharmaceutical formulation of claim 10, wherein the sucrose concentration is 10% ± 1.5% (w/v) and the sodium chloride concentration is 150 mM ± 22.5 mM.

12. The pharmaceutical formulation of any one of claims 1-11, comprising 25 mg/mL ± 3.75 mg/mL antibody, 10mM ± 1.5mM phosphate , pH 6 ± 0.5, 0.2% w/v ± 0.03% polysorbate 20, 10% w/v ± 1.5% sucrose, and 150 mM ± 22.5 mM sodium chloride.

13. The pharmaceutical formulation of any one of claims 1-12, wherein at least 94% of the antibody has native conformation after 28 days of storage at 45°C.

14. The pharmaceutical formulation of any one of claims 1-13, wherein at least 45% of the antibody is the main charge form of the antibody after 28 days of storage at 45°C.

15. The pharmaceutical formulation of any one of claims 1-14, wherein at least 97% of the antibody has native conformation after 28 days of storage at 25°C.

16. The pharmaceutical formulation of any one of claims 1-15, wherein at least 57% of the antibody is the main charge form of the antibody after 28 days of storage at 25°C.

17. The pharmaceutical formulation of any one of claims 1-16, wherein at least 97% of the antibody has native conformation after 28 days of storage at 37°C.

18. The pharmaceutical formulation of any one of claims 1-17, wherein at least 51% of the antibody is the main charge form of the antibody after 28 days of storage at 37°C.

19. The pharmaceutical formulation of any one of claims 1-18, wherein at least 98% of the antibody has native conformation after six months of storage at 5°C.

20. The pharmaceutical formulation of any one of claims 1-19, wherein at least 61% of the antibody is the main charge form of the antibody after six months of storage at 5°C.

21. The pharmaceutical formulation of any one of claims 1-20, wherein the percent relative potency of the antibody after six months of storage at 5°C is at least 100% of the potency of the antibody prior to storage.

22. The pharmaceutical formulation of any one of claims 1-21, wherein at least 99% of the antibody has native conformation after six months of storage at -80°C.

23. The pharmaceutical formulation of any one of claims 1-22, wherein at least 57% of the antibody is the main charge form of the antibody after six months of storage at -80°C.

24. The pharmaceutical formulation of any one of claims 1-23, wherein the percent relative potency of the antibody after six months of storage at -80°C is at least 100% of the potency of the antibody prior to storage.

25. The pharmaceutical formulation of any one of claims 1-24, wherein at least 99% of the antibody has native conformation after six months of storage at -30°C.

26. The pharmaceutical formulation of any one of claims 1-25, wherein at least 57% of the antibody is the main charge variant of the antibody after six months of storage at -30°C.

27. The pharmaceutical formulation of any one of claims 1-26, wherein the percent relative potency of the antibody after six months of storage at -30°C is at least 65% of the potency of the antibody prior to storage.

28. The pharmaceutical formulation of any one of claims 1-27, wherein at least 98% of the antibody has native conformation after six months of storage at -20°C.

29. The pharmaceutical formulation of any one of claims 1-28, wherein at least 60% of the antibody is the main charge variant of the antibody after six months of storage at -20°C.

30. The pharmaceutical formulation of any one of claims 1-29, wherein the percent relative potency of the antibody after six months of storage at -20°C is at least 100% of the potency of the antibody prior to storage.

31. A pharmaceutical formulation comprising (a) 25 mg/mL mL ± 3.75 mg/mL of an anti-Dll4 antibody, (b) 10 mM ± 1.5 mM phosphate, pH 6 ± 0.3, (c) 0.2% ± 0.03% polysorbate 20, (d) 150 mM ± 22.5 mM sodium chloride, and (d) 10% ± 1.5% sucrose, wherein:

(a) the antibody comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5;

(b) the antibody a molecular weight of about 150 kDa; and

(c) about 82% to about 87% of the antibodies are fucosylated.

32. The pharmaceutical formulation of claim 31 consisting of (a) 25 mg/mL ± 3.75 mg/mL of the antibody, (b) 10 mM ± 3 mM phosphate, pH 6 ± 0.5, (c) 0.2% ± 0.03% polysorbate 20, (d) 150 mM ± 22.5 mM sodium chloride, and (e) 10% ± 1.5% sucrose, in water.

33. A pharmaceutical composition of any one of claims 1-32, wherein said composition is contained in a container.

34. The pharmaceutical composition of claim 33, wherein the container is a vial.

35. The pharmaceutical composition of claim 34, wherein the vial is glass.

36. The pharmaceutical composition of claim 33, wherein the container is an IV drip bag.

37. The pharmaceutical composition of claim 36, wherein the bag is made of polyvinyl chloride.

38. The pharmaceutical composition of claim 36, wherein the bag is made of polyolefin.

39. A kit comprising a pharmaceutical composition of any one of claims 1-32, a container, and instructions.

40. The kit of claim 39, wherein the container is a glass vial fitted with a FLUROTEC–coated 4023/50 rubber stopper.

Claims

1. A pharmaceutical formulation consisting essentially of

(a) 25 mg/mL ± 3.75 mg/mL of an anti-Dll4 antibody;

(b) phosphate at a pH of 5.5 to 6.5;

(c) polysorbate 20;

(d) sodium chloride; and

(e) sucrose;

wherein the antibody is a human IgG1 antibody, comprises a heavy chain variable domain (HCVD) of SEQ ID NO: 1 and a light chain variable domain (LCVD) of SEQ ID NO: 5, and has a molecular weight of about 150 kDa; and wherein about 82% to about 87% of the antibodies are fucosylated.

2. A pharmaceutical formulation comprising

(a) 25 mg/mL mL ± 3.75 mg/mL of an anti-D114 antibody,

(b) 10 mM ± 1.5 mM phosphate, pH 6 ± 0.3,

(c) 0.2% ± 0.03% polysorbate 20, (d) 150 mM ± 22.5 mM sodium chloride, and

(e) 10% ± 1.5% sucrose, wherein:

(a) the antibody is a human IgG1 antibody and comprises an HCVD of SEQ ID NO: 1 and an LCVD of SEQ ID NO: 5;

(b) the antibody a molecular weight of about 150 kDa; and

(c) about 82%) to about 87% of the antibodies are fucosylated.

3. The pharmaceutical formulation of claim 2 consisting of

(a) 25 mg/mL + 3.75 mg/mL of the antibody,

(b) 10 mM + 3 mM phosphate, pH 6 ± 0.5,

(c) 0.2% ± 0.03% polysorbate 20,

(d) 150 mM ± 22.5 mM sodium chloride, and

(e) 10% ± 1.5% sucrose, in water.

4. The pharmaceutical formulation of claim 1, wherein the phosphate concentration is 10 mM ± 1.5 mM.

5. The pharmaceutical formulation of claim 1, wherein the polysorbate 20 concentration is 0.2% w/v ± 0.03%.

6. The pharmaceutical formulation of claim 1, wherein the sucrose concentration is 10% ± 1.5% (w/v) and the sodium chloride concentration is 150 mM ± 22.5 mM.

7. The pharmaceutical formulation of claim 1, comprising 25 mg/mL ± 3.75 mg/mL antibody, lOmM ± 1.5mM phosphate , pH 6 ± 0.5, 0.2% w/v + 0.03% polysorbate 20, 10% w/v ± 1.5% sucrose, and 150 mM ± 22.5 mM sodium chloride.

8. The pharmaceutical formulation of any one of claims 1-7, wherein at least 94% of the antibody has native conformation after 28 days of storage at 45°C.

9. The pharmaceutical formulation of any one of claims 1-8, wherein at least 45% of the antibody is the main charge form of the antibody after 28 days of storage at 45°C.

10. The pharmaceutical formulation of any one of claims 1-9, wherein at least 97% of the antibody has native conformation after 28 days of storage at 25°C.

11. The pharmaceutical formulation of any one of claims 1-10, wherein at least 57% of the antibody is the main charge form of the antibody after 28 days of storage at 25°C.

12. The pharmaceutical formulation of any one of claims 1-11, wherein at least 97% of the antibody has native conformation after 28 days of storage at 37°C.

13. The pharmaceutical formulation of any one of claims 1-12, wherein at least 51% of the antibody is the main charge form of the antibody after 28 days of storage at 37°C.

14. The pharmaceutical formulation of any one of claims 1-13, wherein at least 98% of the antibody has native conformation after six months of storage at 5°C.

15. The pharmaceutical formulation of any one of claims 1-14, wherein at least 61% of the antibody is the main charge form of the antibody after six months of storage at 5°C.

16. The pharmaceutical formulation of any one of claims 1-15, wherein the percent relative potency of the antibody after six months of storage at 5°C is 100% of the potency of the antibody prior to storage.

17. The pharmaceutical formulation of any one of claims 1-16, wherein at least

99% of the antibody has native conformation after six months of storage at -80°C.

18. The pharmaceutical formulation of any one of claims 1-17, wherein at least 57% of the antibody is the main charge form of the antibody after six months of storage at -80°C.

19. The pharmaceutical formulation of any one of claims 1-18, wherein the percent relative potency of the antibody after six months of storage at -80°C is 100% of the potency of the antibody prior to storage.

20. The pharmaceutical formulation of any one of claims 1-19, wherein at least 99% of the antibody has native conformation after six months of storage at -30°C.

21. The pharmaceutical formulation of any one of claims 1-20, wherein at least 57% of the antibody is the main charge variant of the antibody after six months of storage at -30°C.

22. The pharmaceutical formulation of any one of claims 1-21, wherein the percent relative potency of the antibody after six months of storage at -30°C is at least 65% of the potency of the antibody prior to storage.

23. The pharmaceutical formulation of any one of claims 1-22, wherein at least 98% of the antibody has native conformation after six months of storage at -20°C.

24. The pharmaceutical formulation of any one of claims 1-23, wherein at least 60% of the antibody is the main charge variant of the antibody after six months of storage at -20°C.

25. The pharmaceutical formulation of any one of claims 1-24, wherein the percent relative potency of the antibody after six months of storage at -20°C is 100% of the potency of the antibody prior to storage.

26. A pharmaceutical composition of any one of claims 1-25 wherein said composition is contained in a container.

27. The pharmaceutical composition of claim 26, wherein the container is a vial.

28. The pharmaceutical composition of claim 27, wherein the vial is glass.

29. The pharmaceutical composition of claim 26, wherein the container is an IV drip bag.

30. The pharmaceutical composition of claim 29, wherein the bag is made of polyvinyl chloride.

31. The pharmaceutical composition of claim 29, wherein the bag is made of polyolefin.

32. A kit comprising a pharmaceutical composition of any one of claims 1-25, a container, and instructions.

33. The kit of claim 32, wherein the container is a glass vial fitted with fluorocarbon-coated 4023/50 rubber stopper.