Claims

1. A pharmaceutical composition comprising crizanlizumab that has light chain and heavy chain amino acid sequences in SEQ ID NO: 10 and SEQ ID NO: 9 respectively, and a variant of crizanlizumab (iso-crizanlizumab), in which amino acid aspartic acid at position 32 of SEQ ID NO: 10 is changed to iso-aspartic acid.

2. The pharmaceutical composition of claim 1 further comprising succinimide of crizanlizumab at position 32 of SEQ ID NO: 10.

3. The pharmaceutical composition of claim 1 or 2, wherein the iso-crizanlizumab consists of homo-iso-crizanlizumab and hetero-iso-crizanlizumab.

4. The pharmaceutical composition of any one of the claims 1 to 3 comprising at least 20% crizanlizumab of the total charge variants in the pharmaceutical composition.

5. The pharmaceutical composition of any one of the claims 1 to 4 comprising at most 50% crizanlizumab of the total charge variants in the pharmaceutical composition.

6. The pharmaceutical composition of any one of the claims 1 to 5 comprising from about 20% to about 50% crizanlizumab of the total charge variants in the pharmaceutical composition.

7. The pharmaceutical composition of any one of the preceding claims further comprising a buffer system, wherein the composition has a pH from about 5.5 to about 7.5.

8. The pharmaceutical composition of claim 7, wherein the pH is about 5.5 to about 7, preferably about 5.5 to about 6.5, preferably about 5.7 to about 6.3.

9. The pharmaceutical composition of claim 7 or 8, wherein the pH is about 5.9 to about 6.1.

10. The pharmaceutical composition of any one of claims the 7-9, wherein the buffer system is citrate buffer.

11. The pharmaceutical composition of any one of the claims 7-9, wherein the buffer system is phosphate buffer.

12. The pharmaceutical composition of any one of the preceding claims further comprising a stabilizer.

13. The pharmaceutical composition of claim 12, wherein the stabilizer is sucrose.

14. The pharmaceutical composition of claim 13, wherein sucrose is in a concentration of 50 mM to 350 mM, preferably 100 mM to 300 mM.

15. The pharmaceutical composition of any one of the preceding claims further comprising an isotonizing agent.

16. The pharmaceutical composition of claim 15, wherein the isotonizing agent is sodium chloride.

17. The pharmaceutical composition of claim 16, wherein sodium chloride is in a concentration of 50 mM to 300 mM.

18. The pharmaceutical composition of any one of the preceding claims further comprising a surfactant.

19. The pharmaceutical composition of claim 18, wherein the surfactant is a non-ionic surfactant.

20. The pharmaceutical composition of claim 18 or 19, wherein the surfactant is polysorbate, preferably polysorbate 80.

21. The pharmaceutical composition of any of the claims 18 to 20, wherein the surfactant, preferably polysorbate, is in a concentration of 0.01% w/v (0.1 mg/mL) to 0.1% w/v (1 mg/mL).

22. The pharmaceutical composition of any one of the preceding claims, wherein ANTIBODY is in a concentration from 5 mg/ml to 50 mg/ml.

23. A pharmaceutical composition comprising antibody in a concentration from about 5 to about 50 mg/ml, and a buffer system, wherein the composition has a pH from about 5.5 to about 7.5.

24. The pharmaceutical composition according to claim 23, wherein the pH is about 5.7 to about 6.3.

25. The pharmaceutical composition according to claim 23 or 24, wherein the buffer system is citrate (e.g. sodium citrate) and/or phosphate (e.g. potassium phosphate).

26. The pharmaceutical composition according to any one of the claims 23-25 further comprising a stabilizer.

27. The pharmaceutical composition according to claim 26, wherein the stabilizer is sucrose.

28. The pharmaceutical composition according to claim 26 or 27, wherein the stabilizer is present in a concentration of about 50 mM to about 300 mM.

29. The pharmaceutical composition according to any one of the claims 23-28 further comprising a non-ionic surfactant.

30. The pharmaceutical composition according to claim 29, wherein the surfactant is polysorbate 80.

31. The pharmaceutical composition according to claim 29 or 30, wherein the surfactant is present in a concentration of about 0.01% w/v (0.1 mg/ml) to 0.1% w/v (1 mg/ml).

32. The pharmaceutical composition according to any one of the claims 23-31 further comprising an isotonizing agent.

33. The pharmaceutical composition according to claim 32, wherein the isotonizing agent is NaCl.

34. The pharmaceutical composition according to claim 32 or 33, wherein the isotonizing agent is present in a concentration of about 50 mM to 300 mM.

35. A pharmaceutical composition comprising antibody (crizanlizumab and any variants thereof) in a concentration from about 5 to about 50 mg/ml, sucrose in a concentration of about 50 mM to about 350mM, and a buffer system, wherein the composition has a pH from about 5.5 to about 7.5, and wherein the buffer system is citrate buffer and/or phosphate buffer.

36. The pharmaceutical composition according to claim 35, wherein the pH of the pharmaceutical composition is about 5.7 to about 6.3, e.g. about 6.0.

37. The pharmaceutical composition according to any one of the preceding claims in a lyophilized form.

38. A lyophilized formulation obtainable by lyophilizing an aqueous formulation, wherein the lyophilized formulation comprises:
a) antibody (crizanlizumab and any variants thereof);
b) a lyoprotectant; and
c) a buffer system.

39. The lyophilized formulation of claim 38 further comprising a surfactant.

40. The lyophilized formulation of claim 39, wherein said surfactant is polysorbate 80.

41. The lyophilized formulation of any one of the claims 38-40, wherein antibody is present in the aqueous formulation in a concentration of about 10 mg/mL to 100 mg/mL.

42. The lyophilized formulation of any one of the claims 38-41, wherein the buffer system is citrate, e.g. sodium citrate.

43. The lyophilized formulation of any one of the claims 38-42 further comprising sucrose and/or mannitol as lyoprotectant.

44. The lyophilized formulation of any of claims 38-43, wherein said aqueous formulation comprises sucrose in a concentration of about 10 mg/mL to 100 mg/mL.

45. The lyophilized formulation of any of claims 43-44, wherein the molar ratio of sucrose to antibody is from about 200 to 1500.

46. The lyophilized formulation of any of claims 38-45 comprising
a) about 25 - 40 w/w %, preferably about 28 to 32 w/w% , of antibody; and
b) about 55 - 75 w/w %, preferably about 65 to 71 w/w % of sucrose,
based on the total weight of the lyophilized formulation.

47. A liquid pharmaceutical composition obtained by reconstituting the lyophilized formulation of any one of the claims 37 to 46.

48. The pharmaceutical composition according to any one of the preceding claims, wherein the IC50 determined by using the pharmaceutical composition is in the range of about 4.6-6.2 µg/ml.

49. The pharmaceutical composition according to claim 48, wherein the IC50 is determined in vitro.

50. A method of treating sickle cell disease, especially preventing Vascular Occlusion Crises (VOC) in a subject in need thereof comprising administering a therapeutically effective dose of antibody (crizanlizumab and any variants thereof) comprised in the pharmaceutical composition according to any one of the claims 1-47 to subject, wherein the therapeutically effective dose is 5mg or 7.5mg per kilogram of the body weight of subject.

51. The method according to claim 50, wherein the first 2 doses are administered 2 weeks apart, followed by administration of the same dose every four weeks.

52. The method of claim 50 or 51, wherein the pharmaceutical composition is administered to a subject by intravenous route.

53. The method of any one of the claims 50 to 52, wherein the therapeutically effective dose is 5mg per kilogram of the weight of subject, wherein the first 2 doses are administered 2 weeks apart, followed by administration of the same dose every four weeks, and wherein one or more or all of the following PK parameters are met:

a) a t_{max} in a range for from 0.4 to 10 hours (h), preferably from 0.55 h to 6.25 h, with a preferred Median of 1.5 to 2.5 h, preferably of 1.92 h, after administrationof said pharmaceutical composition;

b) a C_{max} in the range of, after first dose , 116 ± 91.3 µg/mL; or preferably at steady state at 50 to 200 µg/mL, preferably at 124 ± 31.6 µg/mL;

c) an apparent $t_{1/2}$ in the range of 100 h to 300 h, preferably in the range of 150 h to 210 h, e.g. at about 183 h (7.6 days);

d) an $AUC_{tau, ss}$ in the range of 10 000 to 30 000 µg × h/mL, preferably at week 15 at 20400 µg × h/mL, preferably with a Coefficient of Variance of 23.5 %;

e) a mean clearance at steady state week 15, preferably in a patient with SCD and a body weight of 70 kg, in the range of 10 to 30 mL/h, preferably 15 to 20 mL/h, e.g. at about 17.2 mL/h;

f) a PK trough concentration obtained every 4 weeks in the steady state, especially from week 7 to week 27, range from about 3.78 µg/mL to 9.8 µg/mL.

54. The method of any one of the claims 50 to 52, wherein crizanlizumab and any variants thereof in serum achieves at least 70%, at least 80%, at least 90%, at least 95% inhibition of binding of P-Selectin with PSGL-1.