[0005] Abnormal increases in insulin secretion can lead to hypoglycemia or low blood sugar, a state that may result in significant morbidities including epilepsy and cerebral damage. Drug-induced hypoglycemia can result from administration of sulfonylurea drugs or from an overdose of insulin. A number of rare medical conditions feature non-drug-induced, endogenous hyperinsulinemic hypoglycemia, i.e., low blood glucose caused by the body's excessive production of insulin. These conditions include congenital hyperinsulinism, insulinoma, and hyperinsulinemic hypoglycemia following gastric bypass surgery.

[0006] RZ358 is a monoclonal antibody specific for insulin receptor (INSR) that modulates binding of insulin to the insulin receptor and binds allosterically to INSR without blocking the binding of insulin to the insulin receptor. In a Phase 1 trial, RZ358 was shown to reduce glucose levels in healthy volunteers (Johnson et al., J Clin Endocrinol Metab. 2017 102(8):3021-3028), and in a later study shown to reduced daily periods of hypoglycemia and correct nighttime hypoglycemia in Post Gastric Bypass Hypoglycemia (PGBH) Patients (Hu et al., Journal of the Endocrine Society, Volume 5, Issue Supplement 1, April-May 2021, Pages A328–A329). A recent Phase 2b trial demonstrated improvements in hypoglycemia in congenital hyperinsulinism (CHI) patients receiving antibody therapy (Thornton et al*., RZ358 in Congenital Hyperinsulinism: Results from a Multi-Center, Global, Phase 2b Study (RIZE)*, Pediatric Endocrine Society Annual Meeting 2022).

SUMMARY

[0007] Contemplated herein are high concentration formulations for anti-INSR antibodies, e.g., RZ358, which provide stability of the antibody over time at different storage conditions.

[0008] In one aspect, the disclosure provides a composition comprising an antibody that specifically binds insulin receptor (INSR), at least one amino acid or a salt thereof and a surfactant, wherein the antibody is at a concentration of greater than 150 mg/ml, wherein the anti-INSR antibody comprises (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

[0008a] The disclosure provides a composition comprising an antibody that specifically binds insulin receptor (INSR) at greater than about 150 mg/ml, at least one amino acid or a salt thereof, a surfactant, and a sugar alcohol, wherein the anti-INSR antibody comprises (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth

in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

[0009] In various examples, the anti-INSR antibody comprises: (A) a light chain variable domain comprising a sequence of amino acids at least 80% identical to SEQ ID NO: 2; or (B) a heavy chain variable domain comprising a sequence of amino acids that is at least 80% identical to SEQ ID NO: 1; or (C) a light chain variable domain of (A) and a heavy chain variable domain of (B). In various examples, the heavy chain variable region amino acid sequence is at least 85%, 90%, or 95% or more identical to SEQ ID NO: 1. In various examples, the light chain variable region amino acid sequence is at least 85%, 90% or 95% or more identical to SEQ ID NO: 2.

[0010] In various examples, the anti-INSR antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

[0011] In various examples, the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0012] In various examples, the anti-INSR antibody is an IgG2 antibody.

[0013] In various examples, the anti-INSR antibody is RZ358. In various examples, RZ358 comprises (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2; or a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0014] In various examples, the at least one amino acid or salt thereof is selected from the group consisting of histidine, histidine HCL, methionine, and proline.

[0015] In various examples, the amino acid is histidine. In various examples, the histidine is at a concentration of from about 4 mM to about 25 mM or about 10 mM to about 20 mM. In various examples, the histidine is at a concentration of about 4 ± 1 mM.

[0016] In various examples, the amino acid is histidine HCL. In various examples, the histidine HCL is at a concentration of from about 4 mM to about 25 mM or about 10 mM to about 20 mM. In various examples, the histidine HCL is at a concentration of about 6 ± 1 mM.

[0017] In various examples, the amino acid is methionine. In various examples, the methionine is at a concentration of from about 4 mM to about 25 mM or about 10 mM to about 20 mM. In various examples, the methionine is at a concentration of about 10 ± 2 mM.

[0018] In various examples, the amino acid is proline. In various examples, the proline is at a concentration of from about 200 mM to about 350 mM or about 220 mM to about 300 mM. In various examples, the proline is at a concentration of about 220 ± 70 mM.

[0019] In various examples, the surfactant is Pluronic F68, polysorbate 20 or polysorbate 80. In various examples, the surfactant is at a concentration of about 0.002% (w/v) to about 0.04% (w/v). In various examples, the composition comprises about 0.005% (w/v), 0.010% (w/v), 0.015% (w/v), 0.02% (w/v), 0.025% (w/v), 0.03% (w/v), 0.035% (w/v) or 0.04% (w/v) surfactant. In various examples, the composition comprises about 0.01% (w/v) ± 0.0025% (w/v) polysorbate 20 or polysorbate 80 or a mixture thereof. In various examples, the composition comprises about 0.03% (w/v) ± 0.01% (w/v) Pluronic F68.

[0020] In various examples, the anti-INSR antibody is present in the composition at a concentration from about 150 mg/ml to about 250 mg/mL. In various examples, anti-INSR antibody is present in the composition at a concentration from about 175 mg/ml to about 220 mg/mL. In various examples, anti-INSR antibody is present in the composition at a concentration of about 150 mg/mL to about 200 mg/mL.

[0021] In various examples, the composition is a liquid. In various examples, the composition is lyophilized. In various examples, the composition is a liquid reconstituted from a lyophilized form.

[0022] In various examples, the pH is less than about 6.5. In various examples, the pH is about 5.0 to about 6.5. In various examples, the pH is about 5.4 to about 5.8. In various examples, the pH is about 5.6.

[0023] In various examples, the composition is characterized by a viscosity of about 2 cP to about 10 cP, at 25° C, wherein the concentration of the anti-INSR antibody is greater than about 150 mg/ml.

[0024] In various examples, the composition is isotonic or has an osmolality in a range of about 200 mOsm/kg to about 500 mOsm/kg, or about 225 mOsm/kg to about 400 mOsm/kg, or about 250 mOsm/kg to about 400 mOsm/kg.

[0025] In various examples, the composition comprises less than 5% high molecular weight species after about 4 weeks at 40°C at pH 5.4 to 5.8 as determined by SEC-UHPLC. In various examples, the composition comprises less than 5% low molecular weight species after about 4 weeks at 40°C at pH 5.4 to 5.8 as determined by SEC-UHPLC.

[0026] In another aspect, the disclosure provides a composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, 200 mM to 250 mM proline, 5 mM to 15 mM methionine, and 5 mM to 15 mM histidine, wherein the composition has a pH of about 5.6.

[0026a] In yet another aspect, the disclosure provides a composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 220 mM proline, about 10 mM methionine, and about 4 mM histidine, wherein the composition has a pH of about 5.6.

[0026b] In yet another aspect, the disclosure provides a composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 220 mM proline, about 10 mM methionine, and about 6 mM histidine HCl, wherein the composition has a pH of about 5.6.

[0026c] Provided herein is a composition comprising about 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 200 mM to about 300 mM proline, about 5 mM to about 15 mM methionine, and about 5 mM to about 15 mM histidine, wherein the composition has a pH of about 5.6. Also contemplated is a composition comprising about 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 200 mM to about 270 mM proline, about 5 mM to about 15 mM methionine, and about 5 mM to about 15 mM histidine, wherein the composition has a pH of about 5.6. Further contemplated is a composition comprising about 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 200 mM to about 250 mM proline, about 5 mM to about 15 mM methionine, and about 5 mM to about 15 mM histidine, wherein the composition has a pH of about 5.6.

In various examples, the anti-INSR antibody comprises (A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and (B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 2; or a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10. In various examples, the anti-INSR antibody is RZ358.

[0027] In a further aspect, the disclosure provides an article of manufacture comprising the composition as disclosed herein optionally, comprising 0.5 mL to 5 mL, or 1 to 3 mL of the composition.

[0027a] Further contemplated is an article of manufacture comprising the composition as described herein optionally, comprising about 0.5 mL to about 5 mL, or about 1 mL to about 3 mL of the composition.

[0028] In a further aspect, the disclosure provides a use of the composition as disclosed herein in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling in a subject in need thereof. In yet another aspect, the disclosure provides a composition as disclosed herein for use in therapy.

[0028a] Also contemplated is a method for treating a condition associated with hyperinsulinemia or excess insulin signaling in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition comprising the anti-INSR antibody as described herein. In various examples, condition is selected from the group consisting of: hypoglycemia, insulin sensitivity, cancer, insulinoma, Kaposi' s sarcoma, insulin overdose, nesidioblastosis (KATP-Hl Diffuse Disease, KATP-Hl Focal Disease, or "PHHI"), GDH-Hl (Hyperinsulinism/Hyperammonaemia Syndrome (HI/HA), leucine-sensitive hypoglycemia, diazoxide-sensitive hypoglycemia, islet cell dysregulation syndrome, idiopathic hypoglycemia of infancy, Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), Congenital Hyperinsulinism, acute hypoglycemia due to renal failure, chronic hypoglycemia due to renal failure, and hypoglycemia due to chronic kidney disease. In various examples, the disease is Congenital Hyperinsulinism.

[0029] In various examples, the composition is administered daily, every 2 days, every 3 days, weekly, every 2 weeks, every 3 weeks, twice monthly, monthly, every 2 months, every 3 months or every 6 months. In various examples, the composition is administered for a period of at least 1 month, 2 months, 3 months, 4 months, 6 months, 9 months, 1 year or more.

[0030] In various examples, the composition is administered intravenously. In various examples, the composition is administered subcutaneously.

[0031] The disclosure also provides a composition comprising the anti-INSR antibody as described herein for treating a condition associated with hyperinsulinemia or excess insulin signaling in a subject in need thereof.

[0032] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the invention and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as “one embodiment”, “some embodiments”, “certain embodiments”, “further embodiment”, “specific exemplary embodiments”, and/or “another embodiment”, each of these types of embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination.

WE CLAIM:

1. A composition comprising an antibody that specifically binds insulin receptor (INSR), at least one amino acid or a salt thereof and a surfactant, wherein the antibody is at a concentration of greater than 150 mg/ml, wherein the anti-INSR antibody comprises

(A) a light chain variable domain comprising: (i) a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6; (ii) a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 7; and (iii) a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; and

(B) a heavy chain variable domain comprising: (i) a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 3; (ii) a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 4, and (iii) a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

2. The composition of claim 1, wherein the at least one amino acid or salt thereof is selected from the group consisting of histidine, histidine HCL, methionine, and proline.

3. The composition of claim 1 or 2, wherein the amino acid is histidine.

4. The composition of claim 2 or 3, wherein the histidine is at a concentration of from 4 mM to 25 mM or 10 mM to 20 mM.

5. The composition of any one of claims 2 to 4, wherein the histidine is at a concentration of 4 ± 1 mM.

6. The composition of claim 1 or 2, wherein the amino acid is histidine HCL.

7. The composition of claim 2 or 6, wherein the histidine HCL is at a concentration of from 4 mM to 25 mM or 10 mM to 20 mM.

8. The composition of claim 2, 6 or 7, wherein the histidine HCL is at a concentration of 6 ± 1 mM.

9. The composition of claim 1 or 2, wherein the amino acid is methionine.

10. The composition of claim 2 or 9, wherein the methionine is at a concentration of from 4 mM to 25 mM or 10 mM to 20 mM.

11. The composition of claim 2, 9 or 10, wherein the methionine is at a concentration of 10 ± 2 mM.

12. The composition of any one of claims 1 to 11, wherein the amino acid is proline.

13. The composition of claim 12, wherein the proline is at a concentration of from 100 mM to 350 mM or 200 mM to 300 mM.

14. The composition of claim 12 or 13, wherein the proline is at a concentration of 220 ± 70 mM.

15. The composition of any one of claims 1 to 14, wherein the surfactant is a Pluronic F68 or a polysorbate.

16. The composition of claim 15, wherein the polysorbate is polysorbate 20, polysorbate 80, or a mixture thereof.

17. The composition of any one of claims 1 to 16, comprising the surfactant at a concentration of 0.01% (w/v) to 0.04% (w/v).

18. The composition of claim 17, comprising about 0.015% (w/v), 0.02% (w/v), 0.025% (w/v), 0.03% (w/v) or 0.035% (w/v) or 0.04 % (w/v) surfactant.

19. The composition of any one of claims 1 to 18, comprising 0.03% (w/v) ± 0.01% (w/v) surfactant, optionally wherein the surfactant is Pluronic F68.

20. The composition of any one of claims 1 to 19 comprising methionine, histidine or histidine HCL, and proline.

21. The composition of any one of claims 1 to 20, wherein the anti-INSR antibody comprises:

(A) a light chain variable domain comprising a sequence of amino acids at least 80% identical to SEQ ID NO: 2; or

(B) a heavy chain variable domain comprising a sequence of amino acids that is at least 80% identical to SEQ ID NO: 1; or

(C) a light chain variable domain of (A) and a heavy chain variable domain of (B).

22. The composition of any one of claims 1 to 21, wherein the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

23. The composition of any one of claims 1 to 22, wherein the anti-INSR antibody is an IgG2 antibody.

24. The composition of any one of claims 1 to 23, wherein the anti-INSR antibody is present in the composition at a concentration from 150 mg/ml to 250 mg/mL.

25. The composition of claim 24, wherein the anti-INSR antibody is present in the composition at a concentration from 175 mg/ml to 220 mg/mL.

26. The composition of claim 24, wherein the anti-INSR antibody is present in the composition at a concentration of 150 mg/mL to 200 mg/mL.

27. The composition of any one of claims 1 to 26, wherein the composition is a liquid.

28. The composition of any one of claims 1 to 27, wherein the pH is less than 6.5.

29. The composition of claim 28, wherein the pH is 5.0 to 6.

30. The composition of claim 29, wherein the pH is 5.4 to 5.8.

31. The composition of claim 30, wherein the pH is about 5.6.

32. The composition of any one of claims 27 to 31, characterized by a viscosity of 2 cP to 10 cP at 25° C, wherein the concentration of the anti-INSR antibody is 150 mg/ml or more.

33. The composition of any one of claims 27 to 32, wherein the composition is isotonic or has an osmolality in a range of 200 mOsm/kg to 500 mOsm/kg, or 225 mOsm/kg to 400 mOsm/kg, or 250 mOsm/kg to 400 mOsm/kg.

34. The composition of any one of the preceding claims, wherein the composition comprises less than 5% high molecular weight species after about 4 weeks at 40°C at pH 5.4 to 5.8 as determined by SEC-UHPLC.

35. The composition of any one of the preceding claims, wherein the composition comprises less than 5% low molecular weight species after about 4 weeks at 40°C at pH 5.4 to 5.8 as determined by SEC-UHPLC.

36. A composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, 200 mM to 250 mM proline, 5 mM to 15 mM methionine, and 5 mM to 15 mM histidine, wherein the composition has a pH of about 5.6.

37. A composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 220 mM proline, about 10 mM methionine, and about 4 mM histidine, wherein the composition has a pH of about 5.6.

38. A composition comprising 150-250 mg/mL of an anti-INSR antibody, 0.03% (w/v) Pluronic F68, about 220 mM proline, about 10 mM methionine, and about 6 mM histidine HCl, wherein the composition has a pH of about 5.6.

39. An article of manufacture comprising the composition of any one of the preceding claims optionally, comprising 0.5 mL to 5 mL, or 1 to 3 mL of the composition.

40. Use of the composition of any one of claims 1-38 in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling in a subject in need thereof.

41. The use of claim 40, wherein the condition is selected from the group consisting of: hypoglycemia, insulin sensitivity, cancer, insulinoma, Kaposi’ s sarcoma, insulin overdose, nesidioblastosis (KATP-Hl Diffuse Disease, KATP-Hl Focal Disease, or "PHHI"), GDH-Hl (Hyperinsulinism/Hyperammonaemia Syndrome (HI/HA), leucine-sensitive hypoglycemia, diazoxide-sensitive hypoglycemia, islet cell dysregulation syndrome, idiopathic hypoglycemia of infancy, Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), Congenital Hyperinsulinism, acute hypoglycemia due to renal failure, chronic hypoglycemia due to renal failure, and hypoglycemia due to chronic kidney disease.

42. The use of claim 40 or 41 wherein the disease is Congenital Hyperinsulinism.

43. The use of any one of claims 40 to 42, wherein the composition is to be administered daily, every 2 days, every 3 days, weekly, every 2 weeks, every 3 weeks, twice monthly, monthly, every 2 months, every 3 months or every 6 months.

44. The use of any one of claims 40 to 43, wherein the composition is to be administered intravenously.

45. The use of any one of claims 40 to 44, wherein the composition is to be administered subcutaneously.

46. A composition of any one of claims 1-38 for use in therapy.