

HIGH CONCENTRATION FORMULATIONS FOR ANTI-INSULIN RECEPTOR ANTIBODY AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the priority benefit of U.S. Provisional Patent Application No. 63/ 578,557, filed August 24, 2023, herein incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure relates, in general, to high concentration formulations of an antibody specific for the insulin receptor in the treatment and prevention of hypoglycemia and conditions related to hyperinsulinemia, such as congenital hyperinsulinemia.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0003] The Sequence Listing, which is a part of the present disclosure, is submitted concurrently with the specification as a text file. The name of the text file containing the Sequence Listing is "59393_Seqlisting.xml", which was created on August 24, 2023, and is 9,676 bytes in size. The subject matter of the Sequence Listing is incorporated herein in its entirety by reference.

BACKGROUND

[0004] Insulin is the major hormone for lowering blood glucose levels. The first step in insulin action is the binding of the hormone to the insulin receptor (INSR), an integral membrane glycoprotein, also designated as CD220 or HHF5. When insulin binds to the INSR, the receptor is activated by tyrosine autophosphorylation and the INSR tyrosine kinase phosphorylates various effector molecules, including the insulin receptor substrate-1 (IRS-1), leading to hormone action (Ullrich et al, *Nature* 313: 756-761, 1985; Goldfine et al, *Endocrine Reviews* 8: 235-255, 1987; White and Kahn, *Journal Biol. Chem.* 269: 1-4, 1994). IRS-1 binding, and phosphorylation eventually leads to an increase in the high affinity glucose transporter (Glut4) molecules on the outer membrane of insulin-responsive tissues, including muscle cells and adipose tissue, and to an increase in the uptake of glucose from blood into these tissues. Glut4 mediates the transport of glucose into the cell and a decrease in blood glucose levels.

[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] 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the anti-INSR antibody is an IgG2 antibody.

[0013] In various embodiments, the anti-INSR antibody is RZ358. In various embodiments, 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 embodiments, 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 embodiments, the amino acid is histidine. In various embodiments, 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 embodiments, the histidine is at a concentration of about 4 ± 1 mM.

[0016] In various embodiments, the amino acid is histidine HCL. In various embodiments, 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 embodiments, the histidine HCL is at a concentration of about 6 ± 1 mM.

[0017] In various embodiments, the amino acid is methionine. In various embodiments, 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 embodiments, the methionine is at a concentration of about 10 ± 2 mM.

[0018] In various embodiments, the amino acid is proline. In various embodiments, 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 embodiments, the proline is at a concentration of about 220 ± 70 mM.

[0019] In various embodiments, the surfactant is Pluronic F68, polysorbate 20 or polysorbate 80. In various embodiments, the surfactant is at a concentration of about 0.002% (w/v) to about 0.04% (w/v). In various embodiments, 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 embodiments, the composition comprises about 0.01% (w/v) $\pm$ 0.0025% (w/v) polysorbate 20 or polysorbate 80 or a mixture thereof. In various embodiments, the composition comprises about 0.03% (w/v) $\pm$ 0.01% (w/v) Pluronic F68.

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

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

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

[0023] In various embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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] 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 embodiments, 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 embodiments, the anti-INSR antibody is RZ358.

[0027] 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] 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 embodiments, condition is selected from the group consisting of: hypoglycemia, insulin sensitivity, cancer, insulinoma, Kaposi' s sarcoma, insulin overdose, nesidioblastosis (KATP-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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 embodiments, the disease is Congenital Hyperinsulinism.

[0029] In various embodiments, 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 embodiments, 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 embodiments, the composition is administered intravenously. In various embodiments, 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.

Such features or combinations of features apply to any of the aspects of the invention. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

[0033] The headings herein are for the convenience of the reader and not intended to be limiting. Additional aspects, embodiments, and variations of the invention will be apparent from the Detailed Description and/or Drawings and/or claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Figure 1 shows an accelerated stability of the anti-INSR antibody formulation study main peak as measured by SE-HPLC.

[0035] Figure 2 shows an accelerated stability study of the anti-INSR antibody formulation as measured by HMW SE-HPLC trends.

[0036] Figure 3 shows an accelerated stability study of the anti-INSR antibody formulation and LMW 1 as measured by SE-HPLC.

[0037] Figure 4 shows an accelerated stability study of the anti-INSR antibody formulation and neutral peaks as measured by icIEF.

[0038] Figure 5 illustrates an accelerated stability study of the anti-INSR antibody formulation and acidic peaks as measured by icIEF.

[0039] Figure 6 shows trends in accelerated stability study of the anti-INSR antibody formulation and basic peaks assessed by icIEF.

[0040] Figure 7 illustrates RZ358 low and high molecular weight specie of the anti-INSR antibody formulation % at 40°C as a function of pH.

[0041] Figure 8 shows RZ358 SE-HPLC HMW levels of the anti-INSR antibody formulation as a function of time and temperature.

DETAILED DESCRIPTION

[0042] The present disclosure provides high concentration formulations of a monoclonal antibody specific for the insulin receptor, RZ358, that are stable over long term storage with minimal impurities formed and relative potency of the antibody maintained during storage. Such

stable antibody formulations are useful in the treatment of disorders associated with insulin resistance and conditions related to hyperinsulinemia.

Definitions

[0043] The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

[0044] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise” and variations such as “comprises” and “comprising” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0045] Throughout the specification, where compositions are described as including components or materials, it is contemplated that the compositions can also consist essentially of, or consist of, any combination of the recited components or materials, unless described otherwise. Likewise, where methods are described as including particular steps, it is contemplated that the methods can also consist essentially of, or consist of, any combination of the recited steps, unless described otherwise. The invention illustratively disclosed herein suitably may be practiced in the absence of any element or step which is not specifically disclosed herein.

[0046] The practice of a method disclosed herein, and individual steps thereof, can be performed manually and/or with the aid of or automation provided by electronic equipment. Although processes have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used. For example, the order of various of the steps may be changed without departing from the scope or spirit of the method, unless described otherwise. In addition, some of the individual steps can be combined, omitted, or further subdivided into additional steps.

[0047] The compositions and methods are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described below (including those shown in the figures), unless stated otherwise.

[0048] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique

(e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[0049] It should be understood that every maximum numerical limitation given throughout this specification includes as alternative aspects ranges formed with every corresponding lower numerical limitation, as if such ranges were expressly written. Every minimum numerical limitation given throughout this specification will include as alternative aspects ranges formed with every higher numerical limitation, as if such ranges were expressly written. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein. The dimensions and values disclosed herein should be understood to include disclosure of both the recited value and the corresponding exact numerical, e.g., a value described as “about 10 mM” should be understood to include, as an alternative disclosure, “10 mM.”

[0050] All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

[0051] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below.

[0052] As used in the specification and the appended claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as singular referents unless the context clearly dictates otherwise.

[0053] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure include, but are not limited to: Singleton et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d Ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker Ed., 1988); THE GLOSSARY OF GENETICS, 5th Ed., R. Rieger et al. (Eds.), Springer Verlag (1991); and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991).

[0054] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range. Whenever the term “about” or “approximately” precedes the first numerical value in a series of two or more numerical values, it is understood that the term “about” or “approximately” applies to each one of the numerical values in that series.

[0055] The term “antibody” is used in the broadest sense and includes fully assembled antibodies, tetrameric antibodies, monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), antibody fragments that can bind an antigen (e.g., Fab', F'(ab)2, Fv, single chain antibodies, diabodies), and recombinant peptides comprising the foregoing as long as they exhibit the desired biological activity. An “immunoglobulin” or “tetrameric antibody” is a tetrameric glycoprotein that consists of two heavy chains and two light chains, each comprising a variable region and a constant region. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antibody fragments or antigen-binding portions include, inter alia, Fab, Fab', F(ab')2, Fv, domain antibody (dAb), complementarity determining region (CDR) fragments, CDR-grafted antibodies, single-chain antibodies (scFv), single chain antibody fragments, chimeric antibodies, diabodies, triabodies, tetrabodies, minibody, linear antibody; chelating recombinant antibody, a tribody or bibody, an intrabody, a nanobody, a small modular immune pharmaceutical (SMIP), an antigen-binding-domain immunoglobulin fusion protein, a camelized antibody, a VHH containing antibody, or a variant or a derivative thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as one, two, three, four, five or six CDR sequences, as long as the antibody retains the desired biological activity.

[0056] “Monoclonal antibody” refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

[0057] “Antibody variant” as used herein refers to an antibody polypeptide sequence that contains at least one amino acid substitution, deletion, or insertion in the variable region of the

natural antibody variable region domains. Variants may be substantially homologous or substantially identical to the unmodified antibody.

[0058] A “chimeric antibody,” as used herein, refers to an antibody containing sequence derived from two different antibodies (see, e.g., U.S. Patent No. 4,816,567) which typically originate from different species. Most typically, chimeric antibodies comprise human and rodent antibody fragments, generally human constant and mouse variable regions.

[0059] A “neutralizing antibody” is an antibody molecule which is able to eliminate or significantly reduce a biological function of an antigen to which it binds. Accordingly, a “neutralizing” antibody is capable of eliminating or significantly reducing a biological function, such as enzyme activity, ligand binding, or intracellular signaling.

[0060] “Heavy chain variable region” as used herein refers to the region of the antibody molecule comprising at least one complementarity determining region (CDR) of said antibody heavy chain variable domain. The heavy chain variable region may contain one, two, or three CDR(s) of said antibody heavy chain.

[0061] “Light chain variable region” as used herein refers to the region of an antibody molecule, comprising at least one complementarity determining region (CDR) of said antibody light chain variable domain. The light chain variable region may contain one, two, or three CDR(s) of said antibody light chain, which may be either a kappa or lambda light chain depending on the antibody.

[0062] As used herein, an antibody that “specifically binds” is “antigen specific”, is “specific for” antigen target or is “immunoreactive” with an antigen refers to an antibody or polypeptide binding agent used herein that binds an antigen with greater affinity than other antigens of similar sequence. In one aspect, the antibody, or fragments, variants, or derivatives thereof, will bind with a greater affinity to human antigen as compared to its binding affinity to similar antigens of other, i.e., non-human, species, but polypeptide binding agents that recognize and bind orthologs of the target are within the scope of the methods.

[0063] For example, a polypeptide binding agent that is an antibody or fragment thereof “specific for” its cognate antigen indicates that the variable regions of the antibodies recognize and bind the desired antigen with a detectable preference (e.g., where the desired antigen is a polypeptide, the variable regions of the antibodies are able to distinguish the antigen polypeptide from other known polypeptides of the same family, by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity,

homology, or similarity between family members). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of a polypeptide binding agent, e.g. antibody, for use in the methods herein are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow et al. (Eds), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies for use in the methods can be produced using any method known in the art.

[0064] The term "epitope" refers to that portion of any molecule capable of being recognized by and bound by a selective binding agent at one or more of the antigen binding regions. Epitopes usually consist of chemically active surface groupings of molecules, such as, amino acids or carbohydrate side chains, and have specific three-dimensional structural characteristics as well as specific charge characteristics. Epitopes as used herein may be contiguous or non-contiguous.

[0065] The term "sample" or "biological sample" refers to a specimen obtained from a subject for use in the present methods, and includes urine, whole blood, plasma, serum, saliva, sputum, tissue biopsies, and cerebrospinal fluid.

[0066] The term "therapeutically effective amount" is used herein to indicate the amount of target-specific composition that is effective to ameliorate or lessen symptoms or signs of disease associated with abnormal (e.g., abnormally high or abnormally low) signaling of the signaling complex.

[0067] The terms "treat", "treating" and "treatment" refer to eliminating, reducing, suppressing or ameliorating, either temporarily or permanently, either partially or completely, a clinical symptom, manifestation or progression of an event, disease or condition associated with an inflammatory disorder described herein. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of

the disclosure is directed to a method for determining the efficacy of treatment comprising administering to a patient therapeutic agent in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

Anti-INSR Antibodies

[0068] Provided herein are compositions comprising anti-INSR antibodies formulated in high concentrations (e.g., greater than 150 mg/ml), for example RZ358, in a stable pharmaceutical formulation. Anti-INSR antibodies that negatively modulate the activity of insulin on the insulin receptor are disclosed in U.S. Patents 9,944,698, 10,253,101 and 11,261,247. These negative modulator antibodies allosterically bind to the insulin receptor at a site that does not interfere with insulin binding, but that weakens the binding of insulin to the receptor and reduces signaling through the receptor. This mechanism increases and normalizing blood glucose levels in hyperinsulinemic patients.

[0069] Monoclonal antibodies may be modified for use as therapeutics or diagnostics. One embodiment is a "chimeric" antibody in which a portion of the heavy (H) and/or light (L) chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies, so long as they exhibit the desired biological activity. See U.S. Pat. No. 4,816,567; Morrison et al., 1985, Proc. Natl. Acad. Sci. 81:6851-55.

[0070] In another embodiment, a monoclonal antibody is a "humanized" antibody. Methods for humanizing non-human antibodies are well known in the art. See U.S. Pat. Nos. 5,585,089 and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. Humanization can be performed, for example, using methods described in the art (Jones et al., 1986, Nature 321:522-25; Riechmann et al., 1998, Nature 332:323-27; Verhoeyen et al., 1988, Science 239:1534-36), by substituting at least a portion of a rodent complementarity-determining region for the corresponding regions of a human antibody.

[0071] Chimeric, CDR grafted, and humanized antibodies and/or antibody variants are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a

preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (e.g., human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

[0072] In various embodiments, the disclosure provides an antibody or fragment thereof comprising three heavy chain CDRs having the amino acid sequence set out in SEQ ID NOs: 3-5 and three light chain CDRs have the amino acid sequences set out in SEQ ID NOs: 6-8. In various embodiments, the antibody or fragment thereof binds to i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii).

[0073] In various embodiments, the antibody comprises a polypeptide having an amino acid sequence at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the heavy chain variable region set out in SEQ ID NO: 1 and an amino acid sequence at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the light chain variable region set out in SEQ ID NO: 2, the antibody further comprising at least one, two, three, four, five or all of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3 set out in SEQ ID NOs: 3-8.

[0074] In various embodiments, the anti-INSR antibody or fragment thereof comprises a heavy chain variable region amino acid sequence is set out in SEQ ID NO: 1, and a light chain variable region amino acid sequence is set out in SEQ ID NO: 2.

[0075] In exemplary instances, the anti-INSR antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0076] Also contemplated is an antibody or antibody variant that binds INSR comprising (A) a heavy chain variable domain selected from the group consisting of: (i) a sequence of amino acids at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:1; (ii) a sequence of amino acids encoded by a polynucleotide sequence encoding a polypeptide that is at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:1; (iii) a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide encoding a polypeptide consisting of SEQ ID NO:1; and (B) a light chain variable domain selected from the group consisting of: (i) a sequence of amino acids at least 80% (e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO:2; (ii) a sequence of amino acids encoded by a polynucleotide sequence encoding a polypeptide that is at least 80%

(e.g., about 85%, about 90%, about 95%, greater than 95%) identical to SEQ ID NO: 2; (iii) a sequence of amino acids encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide encoding a polypeptide consisting of SEQ ID NO: 2; or (C) a light chain variable domain of (A) and a heavy chain variable domain of (A), wherein the antibody or antibody variant specifically binds to i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii).

[0077] In various embodiments, the antibody or fragment thereof is a Fab fragment.

[0078] In various embodiments, the antibody or antibody variant thereof is bivalent and selected from the group consisting of a human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a recombinant antibody, an antigen-binding antibody fragment, a single chain antibody, a monomeric antibody, a diabody, a triabody, a tetrabody, a Fab fragment, an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, and an IgG4 antibody. In various embodiments, the anti-INSR antibody is an IgG2 antibody.

[0079] Exemplary sequences for a human IgG2 constant region are available from the Uniprot database as Uniprot number P01859, incorporated herein by reference. Information, including sequence information for other antibody heavy and light chain constant regions is also publicly available through the Uniprot database as well as other databases well-known to those in the field of antibody engineering and production.

[0080] In various embodiments, the antibody, antibody variant or fragment thereof binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii), with an equilibrium dissociation constant K_d of at least 10^{-5} , 10^{-6} , 10^{-7} , 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} M, 10^{-13} M, 10^{-14} M, or 10^{-15} M or less that is capable of weakening the binding affinity between insulin and insulin receptor by at least about 1.5-fold, optionally up to 1000-fold. In certain embodiments, the antibody is capable of weakening the binding affinity between said insulin and insulin receptor by about 2-fold to 500-fold. In various embodiments, the antibody increases the EC_{50} of insulin signaling activity by about 2-fold to 1000-fold, optionally in a pAKT assay.

Formulations

[0081] The present disclosure provides high concentration formulations of anti-INSR antibody RZ358 that are stable over long term storage and at stressed conditions that are useful in the methods described herein. International Patent Application No. PCT/US23/67250 discloses anti-INSR antibody formulations having lower antibody concentrations.

[0082] It is contemplated that the antibody formulation is in liquid or lyophilized form. The formulation may also be a liquid reconstituted from lyophilized form.

[0083] In various embodiments, the composition of the present disclosure is a liquid. In certain aspects, the composition has a pH which is less than about 6.5. In some aspects, the pH is about 5.0 to about 6.0 or about 5.1 to about 5.8, or about 5.5 to about 5.9, e.g., about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, about 5.9 or about 6.0.

[0084] It is contemplated that the formulation herein comprises the anti-INSR antibody at a concentration from about 150 mg/ml to about 250 mg/mL, from about 175 mg/ml to about 225 mg/mL, or from about 200 mg/mL to about 250 mg/mL. In certain embodiments, the formulation comprises the anti-INSR antibody (e.g., RZ358) at a concentration of about 150 mg/ml, about 160 mg/ml, about 170 mg/ml, about 180 mg/ml, about 190 mg/ml, about 200 mg/ml, about 210 mg/ml, about 220 mg/ml, about 230 mg/ml, about 240 mg/ml, or about 250 mg/ml.

[0085] In various embodiments, the formulation comprises one or more of surfactants, stabilizers, amino acids, antioxidants and/or buffering agents, in order to minimize aggregation, oxidation and other protein degradation during storage. Exemplary stabilizers include surfactants and sugar alcohols. Exemplary anti-oxidants include methionine, sugar alcohols, and histidine. Exemplary buffering agents include histidine HCl.

[0086] In various embodiments, the composition comprises histidine. In various embodiments, the histidine is at a concentration of from about 4 mM to about 25 mM, for example about 5 mM to 20 mM, about 10 mM to about 20 mM, or about 8 mM to 15 mM, or about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In various embodiments, the histidine is at a concentration of about 4 ± 1 mM.

[0087] In certain embodiments, the composition comprises histidine HCl. In various embodiments, the histidine HCl is at a concentration of from about 4 mM to about 25 mM, for example about 5 mM to 20 mM, about 10 mM to about 20 mM, or about 8 mM to 15 mM, or about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In various embodiments, the histidine HCL is at a concentration of about 6 ± 1 mM.

[0088] In various embodiments, the composition comprises methionine. In various embodiments, the methionine is at a concentration of from about 4 to about 25 mM, for example about 5 mM to 20 mM, about 10 mM to about 20 mM, or about 8 mM to 15 mM, or about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM, about 10 mM, about 11 mM, about 12 mM, about 13 mM, about 14 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, or about 20 mM. In various embodiments, the methionine is at a concentration of about 10 ± 2 mM.

[0089] In various embodiments, the composition comprises proline. In various embodiments, the proline is at a concentration of from about 100 mM to about 350 mM or about 200 mM to about 300 mM or about 150 to 290 mM. In various embodiments, the proline is at a concentration of about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 140 mM, about 150 mM, about 160 mM, about 170 mM, about 180 mM, about 190 mM, about 200 mM, about 210 mM, about 220 mM, about 230 mM, about 240 mM, about 250 mM, about 260 mM, about 270 mM, about 280 mM, about 290 mM, or about 300 mM. In various embodiments, the proline is at a concentration of about 220 ± 70 mM.

[0090] In some embodiments, the compositions of the present disclosure comprise a surfactant. Surfactants are surface active agents that are amphipathic (having a polar head and hydrophobic tail). Surfactants preferentially accumulate at interfaces, resulting in reduced interfacial tension. Use of a surfactant can also help to mitigate formation of large proteinaceous particles. In some embodiments, the surfactant present in the compositions of the present disclosure is an amphipathic and/or nonionic surfactant. Exemplary surfactants include polyoxyethylene sorbitan fatty acid esters (e.g., polysorbate 20, polysorbate 80), alkylaryl polyethers, e.g., oxyethylated alkyl phenol (e.g., Triton™ X-100), and poloxamers (e.g., Pluronic®, e.g., Pluronic® F68), and combinations of any of the foregoing, either within a class of surfactants or among classes of surfactants. Polysorbate 20 and polysorbate 80 (and optionally mixtures thereof) are contemplated herein. The surfactant in exemplary instances is present in the composition at a concentration of about 0.01% (w/v) to about 0.04% (w/v). For instance, the formulation may comprise about 0.01% (w/v) to about 0.03% (w/v), about 0.02% (w/v) to about 0.04% (w/v), or about 0.02% (w/v) to about 0.03% (w/v) surfactant, e.g., about 0.010% (w/v), about 0.015% (w/v), about 0.02% (w/v), about 0.025% (w/v), about 0.03% (w/v), about 0.035% (w/v), or about 0.04% (w/v). In various embodiments, the composition comprises about 0.03% (w/v) $\pm$ 0.01% (w/v) surfactant, optionally wherein the surfactant is Pluronic F68. In

various embodiments, the composition comprises about 0.03% (w/v) $\pm$ 0.01% (w/v) Pluronic F68.

[0091] In various embodiments, the composition comprises 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 embodiments, the antibody is RZ358.

[0092] If the formulation is in a form intended for administration parenterally, it can be isotonic with blood (about 300 mOsm/kg osmolality). It is contemplated that the osmolality of the composition is in some aspects, 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, about 250 mOsm/kg to about 350 mOsm/kg, or about 275 to about 375 mOsm/kg. In various embodiments, the formulation has an osmolality of about 275 to about 375 mOsm/kg.

[0093] In various embodiments the formulation has a low viscosity. In some embodiments, the formulation 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 about 150 mg/ml or greater.

[0094] In various aspects, the composition of the present disclosure 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, or 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.

[0095] In various embodiments, the composition is provided for storage or use, e.g., in a single-use vial, single-use syringe, or glass, glass-lined, or glass-coated primary container. In various embodiments, the composition is contained in glass vials or syringes for storage.

[0096] In various embodiments, the composition is administered intravenously or subcutaneously. In various embodiments, the composition is administered subcutaneously to a subject, and is isotonic with the intended site of administration.

Methods of Making

[0097] Methods of making the composition of the present disclosure are further provided herein. Using transgenic animals (e.g., mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production such antibodies are produced by immunization with a polypeptide antigen (i.e., having at least 6 contiguous amino acids), optionally conjugated to a carrier. See, e.g., Jakobovits et al., 1993, Proc. Natl.

Acad. Sci. 90:2551-55; Jakobovits et al., 1993, Nature 362:255-58; Bruggermann et al., 1993, Year in Immuno. 7:33. See also PCT App. Nos. PCT/US96/05928 and PCT/US93/06926. Additional methods are described in U.S. Pat. No. 5,545,807, PCT App. Nos. PCT/US91/245 and PCT/GB89/01207, and in European Patent Nos. 546073B1 and 546073A1. Human antibodies can also be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells as described herein.

[0098] Chimeric, CDR grafted, and humanized antibodies and/or antibody variants are typically produced by recombinant methods. Nucleic acids encoding the antibodies are introduced into host cells and expressed using materials and procedures described herein. In a preferred embodiment, the antibodies are produced in mammalian host cells, such as CHO cells. Monoclonal (e.g., human) antibodies may be produced by the expression of recombinant DNA in host cells or by expression in hybridoma cells.

[0099] For recombinant production of the antibody or antibody fragment, the nucleic acid encoding it is isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the monoclonal antibody is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more selective marker genes, an enhancer element, a promoter, and a transcription termination sequence.

[0100] Suitable host cells for cloning or expressing the DNA in the vectors herein are prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, *Enterobacteriaceae* such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41 P disclosed in DD 266,710 published Apr. 12, 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. One preferred *E. coli* cloning host is *E. coli* 294 (ATCC 31,446), although other strains such as *E. coli* B, *E. coli* X1776 (ATCC 31,537), and *E. coli* W3110 (ATCC 27,325) are suitable. These examples are illustrative rather than limiting.

[0101] Eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a

number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[0102] Suitable host cells for the expression of glycosylated antibody are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present disclosure, particularly for transfection of *Spodoptera frugiperda* cells.

[0103] Examples of useful mammalian host cell lines are Chinese hamster ovary cells, including CHOK1 cells (ATCC CCL61), DXB-11, DG-44, and Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77: 4216 (1980)); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, (Graham et al., *J. Gen. Virol.* 36: 59, 1977); baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, (*Biol. Reprod.* 23: 243-251, 1980); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., *Annals N.Y. Acad. Sci.* 383: 44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0104] Host cells are transformed or transfected with expression or cloning vectors for antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In addition, novel vectors and transfected cell lines with multiple copies of

transcription units separated by a selective marker are particularly useful and preferred for the expression of antibodies that bind the desired antigen.

Methods of Use

[0105] Provided herein is use of the high concentration anti-INSR antibody formulations, for example, comprising RZ358, in the treatment of hyperinsulinism/hyperinsulinemia disorders that result from aberrant insulin/INSR signaling and low blood glucose levels.

[0106] Exemplary hyperinsulinism disorders include hypoglycemia, insulin sensitivity, cancer, insulinoma, Kaposi's sarcoma, insulin overdose, nesidioblastosis (KATP-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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.

[0107] Congenital hyperinsulinism (CHI) comprises a group of genetic disorders that are characterized by recurrent episodes of hyperinsulinemic hypoglycemia due to unregulated secretion of insulin by the pancreatic β -cells (Arnoux J., et al. *Orphanet Journal of Rare Diseases* 6:63 (2011); Yorifuji T., *Ann Pediatr Endocrinol Metab* 19:57-68 (2014)). CHI is the most common cause of hyperinsulinemic hypoglycemia in neonatal, infant and childhood periods and is usually diagnosed within the first two years of life. Histopathologically, CHI can present in either diffuse or focal forms. In the diffuse form, all pancreatic β -cells are affected, whereas in focal forms, lesions of abnormal β -cells are (usually) restricted to small areas of the pancreas. The most commonly known causes of CHI are loss-of-function mutations in the genes encoding SUR1 and Kir6.2, subunits of the ATP-sensitive potassium channel (KATP channel), involved in the secretion of insulin in pancreatic β -cells.

[0108] There are currently only a few treatment approaches for persistent Congenital Hyperinsulinemia (CHI) [Arnoux J., et al. *Orphanet Journal of Rare Diseases* 6:63 (2011); Yorifuji T., *Ann Pediatr Endocrinol Metab*. 19:57-68 (2014)]. Diazoxide, a KATP channel activator, inhibits insulin secretion in pancreatic β -cells. The most frequent adverse effect is hypertrichosis (hirsutism). Other side effects include sodium and fluid retention which may precipitate congestive heart failure. Diazoxide is generally ineffective for those patients that have CHI due to KATP channel mutations, one of the most common causes of CHI. Octreotide

is a somatostatin analog that inhibits insulin release. Although not approved for CHI, octreotide is utilized for diazoxide-unresponsive CHI. It is administered subcutaneously (SC) as multiple daily injections or continuously with a pump, or intravenously (IV) because of its short half-life (1 to 2 hours). Common adverse events include gastrointestinal symptoms and gall bladder complications. Partial pancreatectomy is an option for focal lesions and may be curative in a majority of the cases. However, lesions are not always visible or palpable at sites indicated by preoperative imaging. Patients with diffuse forms are primarily treated via continuous glucose feeds or off-label medications. Near-total pancreatectomy has been considered as a treatment, but this is characterized by a high risk of diabetes.

[0109] Iatrogenic hypoglycemia describes the condition and effects of low blood glucose caused by administration of either excessive insulin or its analogues, or medications that stimulate endogenous insulin secretion. Iatrogenic hypoglycemia, fundamentally but not exclusively the result of treatment with an insulin secretagogue or insulin, is a major limiting factor in the glycemic management of diabetes. Iatrogenic hypoglycemia causes recurrent morbidity in most people with T1DM and many with advanced T2DM, and is sometimes fatal. Recurrent episodes of hypoglycemia impair the body's defenses against subsequent falling plasma glucose concentrations and thus cause a vicious cycle of recurrent hypoglycemia.

[0110] Hypoglycemia results in a variety of symptoms including; lack of coordination, confusion, loss of consciousness, seizures, and even death.

[0111] Most episodes of mild hypoglycemia are effectively self-treated by ingestion of glucose tablets or other carbohydrate containing drinks or snacks. More severe symptomatic hypoglycemia also can be treated with oral carbohydrate ingestion. However, when the hypoglycemic patient cannot take oral glucose supplements, because of confusion, unconsciousness or other reasons, parenteral therapy is required. As a non-hospital rescue procedure, injection of the hyperglycemic hormone, glucagon, is sometimes employed, either subcutaneously or intramuscularly by the patient himself or an associate of the patient who has been trained to recognize and treat severe hypoglycemia. In a medical setting, intravenous glucose is the standard parenteral therapy.

Administration and Dosing

[0112] Also contemplated by the disclosure are methods of administering an antibody composition as described herein to treat a hyperinsulinemia disorder described herein.

[0113] Methods of the disclosure are performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian subject, including but not limited to injections, infusions, oral ingestion, intranasal, topical, transdermal, parenteral, inhalation spray, vaginal, or rectal administration. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, and intracisternal injections, as well as catheter or infusion techniques. Administration by, intradermal, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Suitable delivery devices may include those developed for the delivery of insulin (see, e.g., Owens et al *Diabetic Med.* 20(11):886-898, 2003; US20140128803; and Peyser et al. *Annals NY Acad Sci*, 1311:102-123, 2014).

[0114] An antibody composition as described herein may 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. In various embodiments, 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.

[0115] In one embodiment, administration is performed at the site of an affected tissue needing treatment by direct injection into the site or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally. For example, biodegradable microspheres or capsules or other biodegradable polymer configurations capable of sustained delivery of a composition (e.g., a soluble polypeptide, antibody, or small molecule) can be included in the formulations useful in the disclosure implanted at the site.

[0116] Therapeutic compositions may also be delivered to the patient at multiple sites. The multiple administrations may be rendered simultaneously or may be administered over a period of time. In certain cases it is beneficial to provide a continuous flow of the therapeutic composition. Additional therapy may be administered on a period basis, for example, hourly, daily, weekly, every 2 weeks, every 3 weeks, or monthly.

[0117] The amounts of antibody composition in a given dosage will vary according to the size of the individual to whom the therapy is being administered as well as the characteristics of the disorder being treated. In exemplary treatments, it may be necessary to administer about 0.1 to about 25 mg/kg per dose or per day, or from about 0.05 mg/kg to about 10 mg/kg, from about 0.3 mg/kg to about 6 mg/kg, or from about 0.1 mg/kg to about 3 mg/kg. Exemplary doses include, 0.1 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 1 mg/kg, 0.75 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg,

13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg, 21 mg/kg, 22 mg/kg, 23 mg/kg, 24 mg/kg, or 25 mg/kg. Other doses include 1 mg/day, 2.5 mg/day, 5 mg/day, 10 mg/day, 20 mg/day, 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 500 mg/day or 1000 mg/day. These concentrations may be administered as a single dosage form or as multiple doses or continuously.

[0118] Also contemplated in the present methods is the administration of multiple agents, such as an antibody composition described herein in conjunction with a second agent as described herein. Compositions comprising an antibody described herein may be administered to persons or mammals suffering from, or predisposed to suffer from, a condition or disorder to be treated associated with the target polypeptide.

[0119] Concurrent administration of two therapeutic agents does not require that the agents be administered at the same time or by the same route, as long as there is an overlap in the time period during which the agents are exerting their therapeutic effect. Simultaneous or sequential administration is contemplated, as is administration on different days or weeks.

[0120] A second agent may be other therapeutic agents, such as anti-diabetic agents, cytokines, growth factors, other anti-inflammatory agents, anti-coagulant agents, agents that will lower or reduce blood pressure, agents that will reduce cholesterol, triglycerides, LDL, VLDL, or lipoprotein(a) or increase HDL, agents that will increase or decrease levels of cholesterol-regulating proteins, anti-neoplastic drugs or molecules.

[0121] Exemplary agents include, but are not limited to, insulin, glucagon, acarbose, octreotide, verapamil, diazoxide and other agents useful to treat hypoglycemia or side effects associated with hypoglycemia. In various embodiments, an antibody described herein is administered with insulin and/or glucagon, optionally in a delivery device, e.g., a smart delivery device (see, e.g., US20140128803) or dual sensor/pump (e.g., a bionic pancreas system).

[0122] Any of the foregoing antibodies or fragments thereof described herein may be concurrently administered with one or more second agent that is an anti-diabetic agent known in the art or described herein, as adjunct therapy.

[0123] A number of anti-diabetic agents are known in the art, including but not limited to: sulfonylureas (e.g., glimepiride, glisentide, sulfonylurea, AY31637); biguanides (e.g., metformin); alpha-glucosidase inhibitors (e.g., acarbose, miglitol); thiazolidinediones (e.g., troglitazone, pioglitazone, rosiglitazone, glipizide, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, AD 5075, T 174, YM 268, R 102380, NC 2100, NIP 223, NIP 221,

MK 0767, ciglitazone, adaglitazone, CLX 0921, darglitazone, CP 92768, BM 152054); glucagon-like-peptides (GLP) and GLP analogs or agonists of GLP-1 receptor (e.g., exendin) or stabilizers thereof (e.g., DPP4 inhibitors, such as sitagliptin); insulin or analogues or mimetics thereof (e.g., lispro, aspart, glulisine, detemir insulin, egludec insulin, insulin glargine, LANTUS®); and Sodium-glucose Cotransporter-2 (SGLT2) inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin).

[0124] The anti-INSR antibody high concentration formulation described herein, e.g., comprising RZ358, was developed to facilitate subcutaneous administration of larger volumes of the antibody therapeutic. This formulation is intended to optimize the delivery of the anti-INSR antibody, aiming to enhance therapeutic outcomes while minimizing the frequency of administration.

[0125] In various embodiments, the second agent is hyaluronidase. Co-administration of a high concentration anti-INSR antibody formulation described herein, e.g., comprising RZ358, with hyaluronidase could offer significant advantages in terms of drug delivery and patient comfort. Hyaluronidase is an enzyme that may facilitate the dispersion and absorption of injected drugs by breaking down hyaluronic acid in the extracellular matrix. This process could potentially enhance the bioavailability of the antibody, thereby improving its efficacy.

[0126] It is contemplated that the co-administration of anti-INSR antibody high concentration formulation described herein, e.g., comprising RZ358, with hyaluronidase provides the following advantages:

[0127] a. Enhanced bioavailability: by reducing the viscosity of the injection site, hyaluronidase may improve the dispersion and absorption of antibody, leading to better bioavailability of the drug.

[0128] b. Decreased injection site reactions: the use of hyaluronidase could mitigate common adverse effects associated with subcutaneous injections, such as pain, swelling, and redness at the injection site. This enhancement in patient comfort is relevant for adherence to treatment regimens.

[0129] c. Optimized therapeutic outcomes: improved drug absorption and reduced injection site reactions can contribute to more effective therapeutic outcomes, potentially leading to better management of the condition being treated.

[0130] In various embodiments, administration of anti-INSR antibody high concentration formulation described herein, e.g., comprising RZ358, with hyaluronidase improves

bioavailability or adsorption of the antibody, decreases injection site reactions, improves therapeutic outcomes and/or increases patient compliance.

[0131] It is contemplated that the antibody and a second agent may be given simultaneously, in the same formulation. It is further contemplated that the agents are administered in a separate formulation and administered concurrently, with concurrently referring to agents given within 30 minutes of each other.

[0132] In another aspect, the second agent is administered prior to administration of the antibody composition. Prior administration refers to administration of the second agent within the range of one week prior to treatment with the antibody, up to 30 minutes before administration of the antibody. It is further contemplated that the second agent is administered subsequent to administration of the antibody composition. Subsequent administration is meant to describe administration from 30 minutes after antibody treatment up to one week after antibody administration.

[0133] It is further contemplated that other adjunct therapies may be administered, where appropriate. For example, the patient may also be administered a diet or food plan designed for a hypoglycemic patient, surgical therapy, or radiation therapy where appropriate.

[0134] It will also be apparent that dosing may be modified if traditional therapeutics are administered in combination with antibody formulations described herein.

Kits

[0135] The present disclosure also provides a kit including a composition described herein together with a package insert, package label, instructions, or other labeling directing or disclosing any of the methods or embodiments disclosed herein. In certain embodiments, the present disclosure provides kits for producing a single-dose administration unit. In certain embodiments of this disclosure, kits containing single and multi-chambered prefilled syringes (e.g., liquid syringes) are included.

[0136] Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting.

EXAMPLES

Example 1 - Formulation of RZ358 antibody at high concentrations

[0137] RZ358 is a fully human IgG2 monoclonal antibody (mAb) that binds with high affinity to the insulin receptor (INSR). The RZ 358 antibody has a molecular weight of approximately 149 kD and a pI at pH of 7.6. Described herein is development of high concentration (150 mg/mL RZ38 and greater) formulation development stability studies and selection of a unique combination of parenterally approved GRAS excipients aimed to stabilize RZ 358 at high concentrations.

[0138] Methods

[0139] *Buffer exchange:* The buffer exchanges were performed via a combination of dialysis (10,000-fold buffer exchange in a dialysis cassette (Thermo Slide-A-Lyzer® G3 Dialysis Cassettes, 20K MWCO) and centrifugation Centricon concentrator tubes (Millipore, 10K MWCO, centrifuged at 4000 rpm). The concentration of neat samples was determined by measuring sample absorbance using a SoloVPE spectrophotometer with an extinction coefficient of 1.47 mL/(mg*cm). The concentration adjusted solutions were filtered with a syringe driven filter units (Millex-MP, PES, 0.22µm, Millipore). The filtered solutions were filled into 2 cc vials, stoppered, crimped and placed under different stress conditions for stability studies. The fill process was performed under aseptic conditions in a Class II biological safety cabinet.

[0140] *Agitation stress:* RZ358 solutions were filled into 2cc glass vials at capacity of 0.5-1.3mL and sealed with rubber stopper. The filled vials were placed horizontally shaken at 1,000 RPM/25°C for up to 4 hours or until visual changes were observed.

[0141] *Freeze-thaw stress:* The filled samples were placed into a -20°C freezer for at least 24 hours for freezing and then on lab bench until completely thawed. The cycles were repeated for 5 times.

[0142] *Thermal stress:* RZ358 samples were placed at -20°C, 5°C, 30°C and 40°C and pulled at specific time points (normally 1 week, 2 weeks, 1 month, 2 months, 3 months and 6 months) for analysis.

[0143] *Differential Scanning Calorimetry (DSC):* Visual Observation: Visual inspection was performed under a white light source (13W fluorescent tube) against black and white backgrounds. Digital photographs were acquired of all formulations.

[0144] *pH:* pH analysis was performed with a VWR™ SympHony® or Thermo Scientific Orion Star pH Meter, calibrated with three pH standard solutions (pH 4, 7, and 10) with a calibration slope of 97% or higher. Samples were not temperature adjusted and were allowed to equilibrate to ambient temperature prior to pH measurements.

[0145] *Viscosity*: Dynamic viscosity of sterile filtered samples was measured by Rheosense MVroc instrument, utilizing B chip at 1000 sec⁻¹ at 25°C.

[0146] *Osmolality*: Osmolality was measured at time zero of this study. A Model 5600 VAPRO Vapor Pressure Osmometer (Wescor) was used.

[0147] *Sub-visible Particulate Matter Analysis*: HIAC Royco Liquid Particle Counting System was used to analyze subvisible particles. Five runs each at 0.20 mL were measured, with 0.5 mL being consumed by the instrument due to taring prior to each measurement. Particle count calibrations were run at the beginning and end of the sample runs and the first and last runs for each sample were omitted from analysis. All samples were degassed for 30 minutes at 70 torr prior to analysis. *FlowCAM*: The FlowCAM particle imaging system combines optics, electronics, and fluidics for automated analysis of particles. The optical system is used to capture real-time images of the particles in the fluid as they pass through the flow cell. The imaging software provides the ability to assess particle size and morphology. For the digitally subtracted data, repeated particles and circular particles with circle fit >0.87 were removed. All samples were degassed for 30 minutes at 70 torr prior to analysis.

[0148] *SEC-HPLC*: The SEC-HPLC was performed with a Tosoh TSK gel SWxl G3000 7.8 x 300 mm column. The injected sample was eluted isocratically with elution buffer: 50 mM Sodium Phosphate, 400 mM NaCl, pH 6.5 at a flow rate of 0.5 ml/min. Injection load was 25 µg. The run time was 30 minutes. Peaks were detected at 214± 4 nm.

[0149] *CE-SDS (reduced and non-reduced)*: Analysis was performed using Maurice CE-SDS Plus cartridge. Samples were diluted from starting concentrations to 10 mg/mL with Mill-Q water prior to the preparation above. 10 µL of the samples at 10 mg/mL were combined with 90 µL of the Master Mix and prepared for analysis. Non-reduced and reduced samples were incubated for 5 minutes at 70 °C. Sample Load time was 20 seconds, sample load voltage was 4600V, absorbance detection was 220nm. Separation times were 35 minutes for non-reduced and 25 minutes for reduced methods.

[0150] *icIEF*: Analysis was performed using Maurice cIEF cartridge. Samples were diluted from starting concentrations to 3.0 mg/mL with Milli-Q water prior to the preparation above. 20 µL of the samples at 3.0 mg/mL were combined with 180 µL of the Master Mix and prepared for analysis. Samples temperature was 10°C. Injection time was 55 seconds, absorbance detection was 280nm.

[0151] Surfactants can enhance physical stability during freeze thaw and agitation. Experiments were carried out to determine a surfactant that would provide sufficient stability to RZ358 during freeze thaw. Surfactant screening was performed to determine if RZ358 is susceptible to degradation following exposure to agitation and freeze/thaw stress and to assess any stabilizing effects of surfactants by visual analysis, SE-HPLC, and FlowCAM. Table 1 summarizes surfactant screening matrix.

Table 1. Surfactant screen matrix

Surfactant	API (mg/mL)	Buffer
None (No Surfactant)	150	10 mM L-Histidine, 10 mM L-Methionine, 270 mM Sorbitol, pH 5.8
0.03% F68		
0.1% F68		
0.2% F68		
0.01% PS20		
0.005% PS80		
0.01% PS80		

[0152] The stability of 150 mg/mL RZ358 with and without surfactants was studied following agitation and consecutive freeze/thaw cycles. Triplicate vial sets of each formulation were exposed to four (4) hours of agitation at 1,000 RPM on an orbital shaker. Following agitation, stressed samples were also subjected to five (5) consecutive cycles of freezing and thawing, placing vials at -20°C for a minimum of 24 hours before being completely thawed at ambient temperature. One vial set of each formulation acted as unstressed controls. These vials were held at ambient temperature for the same four (4) hour duration that the stressed samples were exposed to agitation.

[0153] Following four hours of agitation and five cycles of 24-hour freezing, each followed by a period of thawing, the stressed surfactant screen samples, as well as their unstressed control counterparts, were photographed and analyzed visually for clarity, coloration, and the presence of visible particulates. Stressed samples that were surfactant-free appeared opaque and displayed a white coloration with a faint yellow hue when held in front of a white background. The unstressed surfactant-free samples appeared opalescent, with a faint yellow coloration, and several small, white particles. Both stressed and unstressed samples containing the various concentrations of F68, PS20, and PS80 were clear, generally free of visible particulates, and displayed a faint yellow tint, regardless of condition.

[0154] SEC-HPLC analysis showed that all stressed samples containing any of the three surfactants at each of the concentrations displayed main peak percentages that differed by $\leq 0.1\%$ compared to the control sample for the same formulation. The stressed samples without surfactant exhibited slight decreases in main peak percentages compared to their respective unstressed control ($\Delta -0.6\%$ to -1.0%), with corresponding increases in High Molecular Weight (HMW) peaks (Table 2).

Table 2.

Sample	HMW Peak (%)	Main Peak (%)	LMW Peak (%)
Surfactant-free Unstressed	0.5	99.4	0.1
Surfactant-free Stressed 1	1.6	98.4	0.0
Surfactant-free Stressed 2	1.4	98.6	0.0
Surfactant-free Stressed 3	1.2	98.8	0.0
0.03% (w/v) F68 Unstressed	0.6	99.4	0.0
0.03% (w/v) F68 Stressed 1	0.5	99.4	0.1
0.03% (w/v) F68 Stressed 2	0.5	99.4	0.1
0.03% (w/v) F68 Stressed 3	0.6	99.4	0.1
0.1% (w/v) F68 Unstressed	0.5	99.4	0.0
0.1% (w/v) F68 Stressed 1	0.5	99.4	0.0
0.1% (w/v) F68 Stressed 2	0.6	99.4	0.0
0.1% (w/v) F68 Stressed 3	0.5	99.4	0.1
0.2% (w/v) F68 Unstressed	0.5	99.4	0.1
0.2% (w/v) F68 Stressed 1	0.5	99.4	0.1
0.2% (w/v) F68 Stressed 2	0.5	99.5	0.0
0.2% (w/v) F68 Stressed 3	0.5	99.4	0.0
0.01% (w/v) PS20 Unstressed	0.6	99.4	0.0
0.01% (w/v) PS20 Stressed 1	0.6	99.4	0.0
0.01% (w/v) PS20 Stressed 2	0.6	99.4	0.0
0.01% (w/v) PS20 Stressed 3	0.5	99.4	0.0
0.005% (w/v) PS80 Unstressed	0.6	99.4	0.0
0.005% (w/v) PS80 Stressed 1	0.5	99.4	0.1
0.005% (w/v) PS80 Stressed 2	0.5	99.4	0.1
0.01% (w/v) PS80 Unstressed	0.5	99.4	0.0
0.01% (w/v) PS80 Stressed 1	0.6	99.4	0.1
0.01% (w/v) PS80 Stressed 2	0.5	99.4	0.1
0.01% (w/v) PS80 Stressed 3	0.5	99.4	0.1

[0155] Sub-visible particle analysis showed that stressed RZ358 formulations containing surfactant displayed only minor increases in subvisible particle counts when compared to unstressed conditions. By contrast, stressed surfactant-free samples displayed higher subtracted subvisible particle counts when compared to their respective unstressed control. Additionally, when comparing all unstressed controls, the surfactant-free sample exhibited

increased subtracted subvisible particle counts compared to samples containing surfactant (Tables 3-9).

Table 3: Surfactant Screening (Surfactant-free) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	Surfactant-free Stressed 1	Surfactant-free Stressed 2	Surfactant-free Stressed 3	Surfactant-free Unstressed
>2 μm	0	12842187	10320327	7312252	93355
>5 μm	0	3018192	2542587	1474774	33713
>10 μm	0	720911	615829	317105	8963
>25 μm	0	25293	18396	18152	280
Subtracted Data (Particles/mL)	MQ Water	Surfactant-free Stressed 1	Surfactant-free Stressed 2	Surfactant-free Stressed 3	Surfactant-free Unstressed
>5 μm	0	2933073	2415020	1427856	31415
>10 μm	0	720333	614492	316618	8853
>25 μm	0	25293	18396	18115	280

Table 4: Surfactant Screening (0.03% (w/v) F68) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.03% (w/v) F68 Stressed 1	0.03% (w/v) F68 Stressed 2	0.03% (w/v) F68 Stressed 3	0.03% (w/v) F68 Unstressed
>2 μm	0	1733	2237	3867	80661
>5 μm	0	513	587	1069	40157
>10 μm	0	98	68	156	17540
>25 μm	0	24	0	12	2201
Subtracted Data (Particles/mL)	MQ Water	0.03% (w/v) F68 Stressed 1	0.03% (w/v) F68 Stressed 2	0.03% (w/v) F68 Stressed 3	0.03% (w/v) F68 Unstressed
>5 μm	0	171	316	661	191
>10 μm	0	24	45	132	45
>25 μm	0	0	0	12	0

Table 5: Surfactant Screening (0.1% (w/v) F68) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.1% (w/v) F68 Stressed 1	0.1% (w/v) F68 Stressed 2	0.1% (w/v) F68 Stressed 3	0.1% (w/v) F68 Unstressed
>2 μm	0	1031	2761	1294	280
>5 μm	0	202	997	329	43
>10 μm	0	81	318	82	22
>25 μm	0	61	66	72	0
Subtracted Data (Particles/mL)	MQ Water	0.1% (w/v) F68 Stressed 1	0.1% (w/v) F68 Stressed 2	0.1% (w/v) F68 Stressed 3	0.1% (w/v) F68 Unstressed
>5 μm	0	91	690	51	43
>10 μm	0	20	274	10	22
>25 μm	0	0	55	0	0

Table 6: Surfactant Screening (0.2% (w/v) F68) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.2% (w/v) F68 Stressed 1	0.2% (w/v) F68 Stressed 2	0.2% (w/v) F68 Stressed 3	0.2% (w/v) F68 Unstressed
>2 μm	0	775	9841	1677	159
>5 μm	0	245	2784	509	60
>10 μm	0	51	1133	50	30
>25 μm	0	31	355	0	30
Subtracted Data (Particles/mL)	MQ Water	0.2% (w/v) F68 Stressed 1	0.2% (w/v) F68 Stressed 2	0.2% (w/v) F68 Stressed 3	0.2% (w/v) F68 Unstressed
>5 μm	0	153	641	150	0
>10 μm	0	41	259	30	0
>25 μm	0	20	68	0	0

Table 7: Surfactant Screening (0.01% (w/v) PS20) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.01% (w/v) PS20 Stressed 1	0.01% (w/v) PS20 Stressed 2	0.01% (w/v) PS20 Stressed 3	0.01% (w/v) PS20 Unstressed
>2 μm	0	2066	1032	4392	767
>5 μm	0	241	204	707	279
>10 μm	0	52	82	169	70
>25 μm	0	21	41	21	0
Subtracted Data (Particles/mL)	MQ Water	0.01% (w/v) PS20 Stressed 1	0.01% (w/v) PS20 Stressed 2	0.01% (w/v) PS20 Stressed 3	0.01% (w/v) PS20 Unstressed
>5 μm	0	136	143	591	100
>10 μm	0	42	41	148	20
>25 μm	0	10	0	0	0

Table 8: Surfactant Screening (0.005% (w/v) PS80) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.005% (w/v) PS80 Stressed 1	0.005% (w/v) PS80 Stressed 2	0.005% (w/v) PS80 Stressed 3	0.005% (w/v) PS80 Unstressed
>2 μm	0	1156	1749	1464	279
>5 μm	0	249	414	424	90
>10 μm	0	50	41	121	60
>25 μm	0	0	10	61	10
Subtracted Data (Particles/mL)	MQ Water	0.005% (w/v) PS80 Stressed 1	0.005% (w/v) PS80 Stressed 2	0.005% (w/v) PS80 Stressed 3	0.005% (w/v) PS80 Unstressed
>5 μm	0	189	259	351	80
>10 μm	0	50	41	121	50
>25 μm	0	0	10	61	0

Table 9: Surfactant Screening (0.01% (w/v) PS80) FlowCAM Results

Raw Data (Particles/mL)	MQ Water	0.01% (w/v) PS80 Stressed 1	0.01% (w/v) PS80 Stressed 2	0.01% (w/v) PS80 Stressed 3	0.01% (w/v) PS80 Unstressed
>2 μm	0	3015	2141	5796	90
>5 μm	0	1611	618	1608	40
>10 μm	0	1123	101	188	0
>25 μm	0	44	0	0	0
Subtracted Data (Particles/mL)	MQ Water	0.01% (w/v) PS80 Stressed 1	0.01% (w/v) PS80 Stressed 2	0.01% (w/v) PS80 Stressed 3	0.01% (w/v) PS80 Unstressed
>5 μm	0	281	417	1362	40
>10 μm	0	30	101	188	0
>25 μm	0	0	0	0	0

[0156] The surfactant screening data indicate that addition of Pluronic F68 at concentrations of 0.03%-0.2%, addition of Polysorbate 20 at concentrations of 0.01% and addition of Polysorbate 80 at concentrations of 0.005%-0.01% successfully protects 150mg/mL RZ358 from aggregation, subvisible and visible particle formation and turbidity.

[0157] To mitigate agitation and freeze thaw induced aggregation, Pluronic F68 concentration of 0.03% was selected for the formulation. While Pluronic F68 was selected for the formulation, the screening showed that use of polysorbate 20 and 80 can also be successfully used to stabilize RZ358.

Example 2 - Analysis of pH on High Concentration RZ358 Formulations

[0158] RZ358 stability as a function of pH was evaluated across a series of product quality attributes. The formulation matrix of varying pHs, from 5.0 to 6.0 is summarized in Table 10. Stability sampling included incubation of formulations at frozen (-20 °C), refrigerated (5 °C), controlled ambient (25 °C), and accelerated (40 °C) storage temperatures, agitation stress and freeze thaw stresses. The temperature storage portion of the study was performed over an eight-week period. pH 5.0 Formulation was eliminated from the screen at time zero due to significant turbidity and gelation observed in the samples. All other samples were analyzed via visual inspection, concentration, pH, osmolality, SE-HPLC, icIEF, CE-SDS under non-reduced and reduced conditions, and FlowCAM.

Table 10. RZ 358 pH screen formulation matrix

Form. No.	Form. Code	Buffer	pH	Tonicity Modifier	Antioxidant	API (mg/mL)	Surfactant
F1	A5.0SM	10 mM Sodium Acetate	5.0	270 mM Sorbitol	10 mM L-Methionine	150	0.03% (w/v) F68
F2	A5.2SM	10 mM Sodium Acetate	5.2	270 mM Sorbitol			
F3	A5.4SM	10 mM Sodium Acetate	5.4	270 mM Sorbitol			
F4	A5.4NM	10 mM Sodium Acetate	5.4	120 mM NaCl			
F5	A5.6SM	10 mM Sodium Acetate	5.6	270 mM Sorbitol			
F6	H5.8SM	10 mM L-Histidine	5.8	270 mM Sorbitol			
F7	H6.0SM	10 mM L-Histidine	6.0	270 mM Sorbitol			
F8	CTRL	10 mM L-Histidine, 10 mM L-Methionine, 270 mM Sorbitol, 0.01% Polysorbate 20, pH 5.8 at 80 mg/mL					

[0159] Agitation and freeze thaw stress arms of the study indicated comparable stability across all formulations as seen by SE-HPLC (aggregation) and CE-SDS (clipping). NaCl containing formulations exhibited some opalescence under both stressed and unstressed conditions. All other formulations displayed faint yellow coloration, across all temperatures and conditions. Subvisible particles counts were the highest in lowest pH formulations (pH 5.2 and 5.4) (Table 11 and Table 12).

Table 11. Sub-visible particle counts under Agitation accelerated stability

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	21727	24492	14283	3243	6036	4166	374
>5 µm	0	9251	10011	5572	860	1585	1251	85
>10 µm	0	1893	4310	1806	264	394	231	20
>25 µm	0	120	788	120	23	15	16	5
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	6429	9263	5378	814	1426	1035	75
>10 µm	0	1778	3711	1801	258	384	215	20
>25 µm	0	115	210	120	17	15	16	5

Table 12. Sub-visible particle counts under Freeze Thaw accelerated stability

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	9981	972	1704	389	613	443	384
>5 µm	0	4978	249	279	145	176	180	95
>10 µm	0	1851	85	135	80	43	75	25
>25 µm	0	140	10	85	50	6	15	0
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	3801	224	155	80	160	170	95
>10 µm	0	1826	80	50	20	43	70	25
>25 µm	0	140	5	15	0	6	10	0

[0160] Size exclusion chromatography was utilized to assess the stability of RZ358 in various candidate formulations after storage at -20°C, 5°C, 25°C, and 40 °C for up to eight weeks. No significant differences were observed between formulations at -20°C, 5°C. At 25°C, most formulations displayed similar main peak percentages ($\Delta \leq 0.8\%$) to time zero results, the lowest-pH formulation (pH 5.2, F2, A5.2SM) exhibited a 4.4% decrease in main peak. At 40°C, pH5.2 formulation exhibited the most pronounced degradation, displaying the largest increase in its low molecular weight (LMW) peak percentage in comparison to other formulations. This formulation also exhibited the largest decrease in its main peak percentage compared to time zero, showing a 21.2% decrease, while the other formulations displayed main peak percentage decreases $\leq 9.7\%$, compared to time zero (Figures 1-3 and Table 13). CE-SDS orthogonal data set was in alignment with SEC, showing greater low molecular weight growth in the low pH formulation.

Table 13: Accelerated Stability Study (T=4 Weeks, 40 °C) SE-HPLC Results

Form. No.	Form. Code	HMW Peak (%)	Main Peak (%)	Main Peak _A (%)	LMW Peak 1 (%)	LMW Peak 2 (%)	Total Area (mAU*s)	Main Peak RT (min)
DS Assay	Control	0.6	99.4	N/A	0.1	N/A	67816	15.8
F2	A5.2SM	1.3	78.1	16.4	3.6	0.5	55960	15.8
F3	A5.4SM	2.0	93.2	3.8	0.9	0.1	57735	15.8
F4	A5.4NM	3.6	95.9	N/A	0.5	N/A	59012	15.8
F5	A5.6SM	1.7	90.8	6.1	1.2	0.1	52533	15.8
F6	H5.8SM	1.9	89.6	6.9	1.4	0.2	59605	15.8
F7	H6.0SM	2.4	94.2	2.7	0.7	N/A	56363	15.8
F8	CTRL	1.4	98.1	N/A	0.5	N/A	65452	15.8

[0161] Samples were analyzed at various timepoints by icIEF to monitor the charge heterogeneity of formulation samples. While most formulations, across all temperatures and conditions displayed comparable stability, pH 5.2 formulation exhibited the largest decreases in Main Peak 1 and Main Peak 2 and largest increase in basic peaks percentages compared to time zero (Figures 4-6).

[0162] Sub-visible particle counts showed a consistently higher particle counts in low pH 5.2 formulation across all temperatures. Additionally, NaCl containing formulation showed increased particle counts at the 25°C 8-week time point (Tables 14-18).

Table 14: Accelerated Stability Study (T=8 Weeks, -20 °C) FlowCAM Results

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	21482	1380	4180	1530	4068	7118	2238
>5 µm	0	10447	239	742	374	888	1740	549
>10 µm	0	3979	75	234	140	245	678	104
>25 µm	0	579	5	20	35	65	244	11
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	8598	214	733	364	853	1715	487
>10 µm	0	3914	75	234	140	230	673	104
>25 µm	0	579	5	20	35	55	244	11

Table 15: Accelerated Stability Study (T=8 Weeks, 5 °C) FlowCAM Results

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	931737	1186	1077	787	319	962	629
>5 µm	0	770899	379	170	264	100	254	115
>10 µm	0	172633	115	50	70	30	100	10
>25 µm	0	8800	20	10	20	0	10	0
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	595865	344	135	254	95	254	115
>10 µm	0	171433	115	45	70	30	100	10
>25 µm	0	8284	20	10	20	0	10	0

Table 16: Accelerated Stability Study (T=8 Weeks, 25 °C) FlowCAM Results

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	NA	1679	138586	1312	1315	1102	2538
>5 µm	0	NA	598	114133	559	613	364	628
>10 µm	0	NA	224	25655	220	244	135	135
>25 µm	0	NA	50	46	50	70	5	15
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	NA	598	60977	549	608	364	579
>10 µm	0	NA	224	25610	220	244	135	135
>25 µm	0	NA	50	46	50	70	5	15

Table 17: Accelerated Stability Study (T=4 Weeks, 40 °C) FlowCAM Results

Raw Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>2 µm	0	143880	5048	1132	2667	1307	2153	2016
>5 µm	0	5726	877	389	693	419	753	503
>10 µm	0	880	224	105	140	90	155	143
>25 µm	0	56	5	5	30	10	10	31
Subtracted Data (Particles/container)	MQ Water	F2	F3	F4	F5	F6	F7	F8
>5 µm	0	5656	837	369	663	389	668	317
>10 µm	0	875	219	100	135	90	140	106
>25 µm	0	56	5	5	30	10	10	13

[0163] NaCl was eliminated as a potential future excipient for stabilizing RZ358 due to multiple negative impacts to RZ 358 product quality attributes. Additionally, pH 5.2 condition was eliminated due to instability. To minimize low molecular weight and aggregation in RZ358, pH 5.6 was selected for 150mg/mL RZ358 formulation, as demonstrated in Figure 7.

Example 3 - Analysis of excipients to minimize viscosity and stability of RZ358

[0164] Formulations of RZ358 at higher concentrations were assessed for long-term stability and potency. 150 mg/mL RZ358 formulations containing a series of excipients were evaluated across a series of product quality attributes. Table 18 summarizes a combination of sugars and amino acids screened. Stability sampling included incubation of formulations at frozen (-20 °C), refrigerated (5 °C), controlled ambient (25 °C), and accelerated (40 °C) storage temperatures.

Table 18. Excipient formulation screening matrix

Form. No.	Form. Code	Sugar	Amino Acid	API (mg/mL)
Base Formulation		10 mM L-Histidine, 10 mM L-Methionine, 0.03% F68, pH 5.6		
F1	HPM	–	250 mM L-Proline	150
F2	HSPM	135 mM Sorbitol	135 mM L-Proline	
F3	HRM	–	135 mM Arginine-HCl	
F4	HSRM	135 mM Sorbitol	70 mM Arginine-HCl	
F5	HGM	–	250 mM Glycine	
F6	HSGM	135 mM Sorbitol	135 mM Glycine	
F7	HREM	–	135 mM L-Arginine 143 mM Glutamic Acid	
F8	HTM	270 mM Trehalose	–	
F9	CTRL	270 mM Sorbitol	–	

[0165] Viscosity measurements were performed at 25°C at a sheer rate of 1000 Sec⁻¹ and are summarized in Table 19. Arginine and proline containing formulations decreased formulation viscosity most effectively, as compared to other excipients.

Table 19. RZ358 Viscosity as a function of excipients.

Excipient	Viscosity (cP)
Proline	6.785
Proline / Sorbitol	7.089
Arginine	6.338
Arginine /Sorbitol	7.393
Glycine	7.698
Glycine / Sorbitol	7.699
Arginine / Glutamic Acid	6.892
Trehalose	8.678
Sorbitol	7.773

[0166] Appearance observations showed that arginine containing formulations were opalescent across all temperatures and time points examined. After 8-week incubation at 25°C,

arginine and arginine/sorbitol formulations showed pH drift from T=0 and increased subvisible particle counts (Table 20). Thus, despite exhibiting low viscosity, arginine containing formulations resulted in significant RZ358 instability across a multiple product attributes.

Table 20. 150 mg/mL RZ358 stability in arginine containing formulations.

Excipient	pH, T=0	pH, 25°C, T8 wks	10 µm cts/mL 4°C T4wks	25 µm cts/mL, 4°C T4wks	Appearance, across TP/temps
Proline	5.7	5.7	124	14	Clear
Proline/Sorbitol	5.6	5.6	134	30	Clear
Arginine	5.7	5.9	6276	1360	opalescence
Arginine/Sorbitol	5.8	6.2	17566	4754	opalescence
Glycine	5.7	5.7	38	4	Clear
Glycine/Sorbitol	5.6	5.6	158	26	Clear
Arginine/Glutamic Acid	5.6	5.6	56	0	opalescence
Trehalose	5.7	5.7	30	0	Clear
Sorbitol	5.7	5.7	98	14	Clear

[0167] Size exclusion chromatography was utilized to assess the stability of RZ358 in various candidate formulations after storage at -20°C, 5°C, 25°C, and 40 °C for up to eight weeks. Table 21 and Figure 8 show RZ358 aggregate levels as a function of time and temperature. While no excipient-based impact was observed at lowest temperatures, proline based formulation showed highest main peak levels at 25°C, and 40 °C compared to other formulations.

Table 21. 150 mg/mL RZ358 HMW at -20°C, 5°C, 25°C, and 40 °C at T=8weeks

	T=0, Main Peak (%)	T8W, - 20°C Main Peak (%)	T8W, 5°C Main Peak (%)	T8W, 25°C Main Peak (%)	T4W, 40°C Main Peak (%)
Proline	99.2	99.2	99.2	99.0	98.1

Proline/Sorbitol	99.2	99.3	99.3	99.0	98.0
Arginine	99.3	99.2	99.3	99.1	97.8
Arginine/Sorbitol	99.2	99.3	99.2	98.9	97.8
Glycine	99.2	99.2	99.3	98.9	97.7
Glycine/Sorbitol	99.3	99.3	99.3	98.9	97.7
Arginine/Glutamic Acid	99.3	99.4	99.3	99.1	97.8
Trehalose	99.2	99.2	99.2	98.9	97.7
Sorbitol	99.2	99.3	99.2	98.8	97.6

[0168] No significant excipient impacts were observed in RZ358 stability as examined by icIEF and FlowCAM. CE-SDS data was in orthogonal agreement with SE-HPLC trends, as seen in other screens. Based on the excipient screening data, proline was selected as the amino acid of choice to most optimally protect RZ358 against aggregation and to minimize viscosity.

[0169] In view of the experimental evidence above, a formulation comprising the following excipients is advantageous for high concentration formulations of RZ358 (e.g., 150 mg/ml or greater):

Excipient/condition	concentration	Primary function
Pluronic F68 (poloxamer 188)	0.03%	Enhance physical stability during freeze thaw and agitation
L-methionine	10mM	To minimize oxidation
Proline	220mM	To minimize viscosity, to minimize aggregation and as a tonicity modifier
L-histidine/histidine HCl	4mM/6mM (0.621g/L/1.26g/L)	Buffering agent and to minimize oxidation
pH target	5.6	Optimal stability across critical quality attributes, to minimize aggregation and clipping

[0170] Preferred embodiments of this disclosure are described herein. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the disclosure to be practiced otherwise than as specifically described herein. Accordingly, this disclosure includes all modifications and

equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the disclosure unless otherwise indicated herein or otherwise clearly contradicted by context.

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 about 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 about 4 mM to about 25 mM or about 10 mM to about 20 mM.
5. The composition of any one of claims 2 to 4, wherein the histidine is at a concentration of about 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 about 4 mM to about 25 mM or about 10 mM to about 20 mM.
8. The composition of claim 2, 6 or 7, wherein the histidine HCL is at a concentration of about 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 about 4 mM to about 25 mM or about 10 mM to about 20 mM.
11. The composition of claim 2, 9 or 10, wherein the methionine is at a concentration of about 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 about 100 mM to about 350 mM or about 200 mM to about 300 mM.
14. The composition of claim 12 or 13, wherein the proline is at a concentration of about 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 about 0.01% (w/v) to about 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 about 0.03% (w/v) $\pm$ 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 about 150 mg/ml to about 250 mg/mL.
25. The composition of claim 24, wherein the anti-INSR antibody is present in the composition at a concentration from about 175 mg/ml to about 220 mg/mL.
26. The composition of claim 24, wherein the anti-INSR antibody is present in the composition at a concentration of about 150 mg/mL to about 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 about 6.5.
29. The composition of claim 28, wherein the pH is about 5.0 to about 6.
30. The composition of claim 29, wherein the pH is about 5.4 to about 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 about 2 cP to 10 cP at 25° C, wherein the concentration of the anti-INSR antibody is about 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 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.
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 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.
37. A composition comprising about 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 about 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 about 0.5 mL to about 5 mL, or about 1 to about 3 mL of the composition.
40. 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 of any one of claims 1-38.

41. The method 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-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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 method of claim 40 or 41 wherein the disease is Congenital Hyperinsulinism.

43. The method of any one of claims 40 to 42, wherein 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.

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

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

46. A composition of any one of claims 1-38 for treating a condition associated with hyperinsulinemia or excess insulin signaling in a subject in need thereof.

47. The composition of claim 46, wherein the condition is selected from the group consisting of: hypoglycemia, insulin sensitivity, cancer, insulinoma, Kaposi' s sarcoma, insulin overdose, nesidioblastosis (KATP-HI Diffuse Disease, KATP-HI Focal Disease, or "PHHI"), GDH-HI (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.

48. The composition of claim 46 or 47, wherein the disease is Congenital Hyperinsulinism.