

HIGHLY CONCENTRATED LIQUID FORMULATIONS FOR ANTIBODIES**CROSS REFERENCE TO RELATED APPLICATION**

[01] This application claims the benefit of priority from U.S. Provisional Patent Application Number 63/621,417, filed January 16, 2024, the contents of which are herein incorporated by reference in their entirety.

REFERENCE TO A SEQUENCE LISTING

[02] The instant application contains a Sequence Listing which is hereby incorporated by reference in its entirety. Said Sequence Listing, created on January 10, 2025 is named 2790B-116-SEQ-Listing.XML and is 58774 bytes in size.

FIELD OF THE DISCLOSURE

[03] The present disclosure relates to a stable liquid formulation containing a high concentration of an antigen-binding protein, such as a monoclonal antibody, suitable for subcutaneous administration. In particular, the formulation is characterized by comprising a therapeutic anti-CD38 antibody, a histidine buffer, trehalose, methionine, and a surfactant, and having a pH in the range of about 5.5 to about 6.5. In addition, the present disclosure provides methods of making and using such formulations for the treatment of a disease or disorder, such as an inflammatory disease or disorder, *e.g.*, an autoimmune disease or disorder.

BACKGROUND

[04] The pharmaceutical use of antibodies is constantly increasing. In many instances, therapeutic antigen-binding proteins, such as monoclonal antibodies, are injected via the intravenous route. Alternative administration pathways include subcutaneous or intramuscular injection, which offer potential advantages, such as reduced dosage volumes, improved patient compliance and ease of administration. However, such administration routes require use of formulations containing high protein concentration. The advantage of subcutaneous administration is that it allows the medical practitioner to perform it in a relatively short intervention with the patient. Moreover, the patient can be trained to perform the subcutaneous injection by themselves. Such self-administration is particularly useful during maintenance dosing because no continuous hospital care is needed, thereby reducing utilization of medical resources.

[05] However, due to the limited volume of formulation needed for subcutaneous injection, the required antibody concentrations exceed concentrations greater than 100 mg/mL. This poses several technical challenges. For example, solutions with a high concentration of protein tend to exhibit high viscosity due to macromolecular properties of proteins and intermolecular interactions between them. Viscosity is also an important optimization factor for the delivery and manufacturing of highly concentrated protein formulations. Generally, higher viscosity of the formulation affects its syringeability and results in longer administration times via syringe and needle. Most commercially available auto-injectors are limited to solution viscosities of 20 mPa•s or less. Therefore, viscosity is an important factor for the development of a highly concentrated liquid formulation containing therapeutic antibodies.

[06] Further, high concentration liquid formulations containing antibodies may exhibit problematic degradation that results in the generation of protein aggregates. Such physical instability results from changes in secondary and higher order structure of proteins and can have an impact on the commercial viability and efficacy of pharmaceutical protein formulations. Protein stability can be improved by including excipients that interact with the protein in solution to keep the protein stable, soluble, and unaggregated (*e.g.*, monomeric). For example, salt compounds such as NaCl and KCl, among other ionic species, are frequently used as additives in protein formulations. By binding to proteins in a non-specific fashion, they minimize protein denaturation and increase thermal stability. Opalescence is another proxy for physical instability of a formulation - the presence of aggregates or liquid-liquid phase separation in solution leads to increased opalescence of antibody formulations. Additionally, long formulation storage times may adversely affect the bioactivity of antibodies, for example, due to deamidation of amino acid residues.

[07] The present disclosure addresses various problems associated with the production of stable high concentration liquid antibody formulations.

SUMMARY OF THE DISCLOSURE

[08] The present disclosure is based, in part, on the identification of a highly concentrated liquid formulation (HCLF) for an anti-CD38 antibody which maintains the stability of the antibody over time and which is suitable for subcutaneous administration. Accordingly, the present disclosure provides a liquid formulation containing a high concentration of the anti-CD38 antibody, felzartamab (HIB202/MOR202), or an antigen-binding fragment thereof for which reconstitution of a lyophilized formulation is not necessary.

[009] In an aspect, the disclosure provides a liquid pharmaceutical formulation, the formulation comprising: (a) an anti-CD38 or antigen-binding fragment thereof; (b) a sugar; (c); a non-ionic surfactant; (d) a stabilizer; and I a histidine buffer having a pH between 5.0 and 7.0 (*e.g.*, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0).

[010] In certain embodiments, the anti-CD38 antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising a complementarity determining region 1 (HCDR1) having the amino acid sequence of SEQ ID NO: 1, a HCDR2 having the amino acid sequence of SEQ ID NO: 2, and a HCDR3 having the amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a complementarity determining region 1 (LCDR1) having the amino acid sequence of SEQ ID NO: 4, a LCDR2 having the amino acid sequence of SEQ ID NO: 5 and a LCDR3 having the amino acid sequence of SEQ ID NO 6. In certain embodiments, the anti-CD38 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO: 7 and a VL comprising the amino acid sequence of SEQ ID NO: 8. In certain embodiments, the anti-CD38 antibody or antigen-binding fragment thereof is felzartamab or antigen-binding fragment thereof.

[011] In certain embodiments, the formulation includes the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 100 mg/mL to about 200 mg/mL (*e.g.*, about 100 to about 200 mg/mL, about 110 to about 190 mg/mL, about 120 to about 180 mg/mL, about 130 to about 170 mg/mL, about 140 to about 160 mg/mL, and about 145 to about 155 mg/mL). In certain embodiments, the formulation includes the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL. In certain embodiments, the formulation includes the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL.

[012] In certain embodiments, the sugar is trehalose or sucrose. In certain embodiments, the sugar is trehalose and is included in the formulation at a concentration in the range of about 200 to about 300 mM (*e.g.*, about 200 to about 300 mM, about 210 to about 290 mM, about 220 to about 280 mM, about 230 to about 270 mM, about 240 to about 260 mM). In certain embodiments, the sugar is trehalose and is included in the formulation at a concentration of about 240 nM. In certain embodiments, the sugar is trehalose and is included in the formulation at a concentration of 240 nM. In certain embodiments, the sugar is sucrose and is included in the formulation at a concentration in the range of about 200 to about 300 mM (*e.g.*, about 200 to about 300 mM, about 210 to about 290 mM, about 220 to about 280 mM, about 230 to about 270 mM, about 240 to about 260 mM). In certain embodiments, the sugar is sucrose and is included

in the formulation at a concentration of about 260 nM. In certain embodiments, the sugar is sucrose and is included in the formulation at a concentration of 260 nM.

[013] In certain embodiments, the non-ionic surfactant is poloxamer 188 or polysorbate 20. In certain embodiments, the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration in the range of 0.1% (v/v) to 1.0% (v/v) (*e.g.*, 0.1% to 1.0% v/v, 0.2% to 0.9% v/v, 0.3% to 0.8% v/v, 0.4% to 0.7% v/v, 0.5% to 0.6% v/v). In certain embodiments, the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration of 0.5% (v/v). In certain embodiments, the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration in the range of 0.01% (v/v) to 1.0% (v/v) (*e.g.*, 0.1% to 1.0%, 0.2% to 0.9% v/v, 0.3% to 0.8% v/v, 0.4% to 0.7% v/v, 0.5% to 0.6% v/v). In certain embodiments, the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration of 0.1% (v/v). In certain embodiments, the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration in the range of 0.1% (w/v) to 1.0% (w/v) (*e.g.*, 0.1% to 1.0% w/v, 0.2% to 0.9% w/v, 0.3% to 0.8% w/v, 0.4% to 0.7% w/v, 0.5% to 0.6% w/v). In certain embodiments, the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration of 0.5% (w/v). In certain embodiments, the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration in the range of 0.01% (w/v) to 1.0% (w/v) (*e.g.*, 0.1% to 1.0% w/v, 0.2% to 0.9% w/v, 0.3% to 0.8% w/v, 0.4% to 0.7% w/v, 0.5% to 0.6% w/v). In certain embodiments, the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration of 0.1% (w/v).

[014] In certain embodiments, the stabilizer is methionine and is included in the formulation at a concentration in the range of 5 mM to 20 mM (*e.g.*, 5 to 20 mM, 6 to 19 mM, 7 to 18 mM, 8 to 17 mM, 9 to 16 mM, 10 to 15 mM). In certain embodiments, the stabilizer is methionine and is included in the formulation at a concentration of 10 mM.

[015] In certain embodiments, the histidine buffer is included in the formulation at a concentration in the range of 5 to 20 mM (*e.g.*, 5 to 20 mM, 6 to 19 mM, 7 to 18 mM, 8 to 17 mM, 9 to 16 mM, 10 to 15 mM). In certain embodiments, the histidine buffer is included in the formulation at a concentration of 10 mM. In certain embodiments, the histidine buffer has a pH of about 5.5 to about 6.0 (*e.g.*, about 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0). In certain embodiments, the histidine buffer has a pH of about 5.5. In certain embodiments, the histidine buffer has a pH of 5.5. In certain embodiments, the histidine buffer has a pH of about 6.0. In certain embodiments, the histidine buffer has a pH of 6.0.

[016] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) methionine at a concentration of about 10 mM;
- d) poloxamer 188 at a concentration of about 0.5% (w/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[017] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) poloxamer 188 at a concentration of 0.5% (w/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[018] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) poloxamer 188 at a concentration of 0.5% (w/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[019] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) sucrose at a concentration of about 260 mM;
- c) methionine at a concentration of about 10 mM;
- d) polysorbate 20 at a concentration of about 0.1% (w/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 6.0.

[020] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) sucrose at a concentration of 260 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (w/v); and

- e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.

[021] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) sucrose at a concentration of 260 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (w/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.

[022] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) methionine at a concentration of about 10 mM;
- d) polysorbate 20 at a concentration of about 0.1% (w/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[023] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (w/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[024] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (w/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[025] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) poloxamer 188 at a concentration of about 0.5% (w/v); and

d) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[026] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) poloxamer 188 at a concentration of 0.5% (w/v); and
- d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[027] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) poloxamer 188 at a concentration of 0.5% (w/v); and
- d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[028] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) methionine at a concentration of about 10 mM;
- d) poloxamer 188 at a concentration of about 0.5% (v/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[029] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) poloxamer 188 at a concentration of 0.5% (v/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[030] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) poloxamer 188 at a concentration of 0.5% (v/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[031] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) sucrose at a concentration of about 260 mM;
- c) methionine at a concentration of about 10 mM;
- d) polysorbate 20 at a concentration of about 0.1% (v/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 6.0.

[032] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) sucrose at a concentration of 260 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (v/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.

[033] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) sucrose at a concentration of 260 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (v/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.

[034] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) methionine at a concentration of about 10 mM;
- d) polysorbate 20 at a concentration of about 0.1% (v/v); and
- e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[035] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (v/v); and

- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[036] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) methionine at a concentration of 10 mM;
- d) polysorbate 20 at a concentration of 0.1% (v/v); and
- e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[037] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
- b) trehalose at a concentration of about 240 mM;
- c) poloxamer 188 at a concentration of about 0.5% (v/v); and
- d) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.

[038] In certain embodiments, the formulation comprises:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) poloxamer 188 at a concentration of 0.5% (v/v); and
- d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[039] In certain embodiments, the formulation consists of:

- a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
- b) trehalose at a concentration of 240 mM;
- c) poloxamer 188 at a concentration of 0.5% (v/v); and
- d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

[040] In certain embodiments, the formulation has an antibody monomer content that is at least 95.8% after 6 months of storage at 4-8°C. In certain embodiments, the formulation does not exhibit visible proteinaceous particles. In certain embodiments, the formulation has an opalescence after 3 months of storage at 25°C that is no more than 6 nephelometric turbidity units (NTU). In certain embodiments, the formulation has an opalescence after 6 months of storage at 25°C that is no more than 6 NTU. In certain embodiments, the formulation does not exhibit a change in color after six months of storage at 25°C. In certain embodiments, the formulation does not affect binding of the anti-CD38 or antigen-binding fragment thereof to CD38.

[041] In certain embodiments, the formulation is for use in the treatment of a disease or disorder. In certain embodiments, the disease or disorder is an inflammatory disease or disorder. In certain embodiments, the inflammatory disease or disorder is an autoimmune disease or disorder. In certain embodiments, the formulation is formulated for subcutaneous administration.

BRIEF DESCRIPTION OF THE DRAWINGS

[042] **FIG. 1** shows a schematic illustrating an overview of antibody formulation development and nomenclature of formulations.

[043] **FIG. 2** shows a bar graph illustrating aggregation tendency results of DOE1 screening ($\alpha=0.05$) of various excipients determined by ultra high-performance size exclusion chromatography (UHP-SEC) after storage for two weeks at 50°C, as calculated by multiple linear regression (MLR) analysis.

[044] **FIG. 3** shows a bar graph illustrating monomer contents of screening formulations (Formulations 1-6) as a function of protein concentration determined by UHP-SEC. Samples were assessed at 2 mg/mL, 80 mg/mL, and >150 mg/mL of antibody (*:no data available).

[045] **FIGS. 4A and 4B** show bar graphs illustrating felzartamab (HIB202/MOR202) monomer content within detergent screening study after one week of shaking and dilution in 0.9% NaCl and one night of incubation at 25°C / 60% r.h. (**FIG. 4A**) and after two weeks of storage at 2-8°C and 40°C / 75% r.h. (**FIG. 4B**), as measured by UHP-SEC.

[046] **FIGS. 5A-5C** show bar graphs illustrating subvisible particle levels determined by light obscuration (LO) for particle size class $\geq 2 \mu\text{m}$ (**FIG. 5A**), $\geq 10 \mu\text{m}$ (**FIG. 5B**), $\geq 25 \mu\text{m}$ (**FIG. 5C**).

[047] **FIG. 6** shows a bar graph demonstrating effect of various formulation components (arginine, “Arg”; trehalose, “Tre”) and parameters (pH) on melting temperature of felzartamab as calculated using MLR analysis. pH was screened across a range of 5.5 to 6.2; arginine was screened across a concentration range of 0 to 90 mM, and trehalose was screened across a concentration range of 135 to 240 mM.

[048] **FIG. 7** shows a bar graph illustrating dynamic viscosity determined for the high concentration liquid formulation (HCLF) optimization study.

[049] **FIG. 8A** shows a plot illustrating effect of arginine (in mM) on viscosity attributes of felzartamab. **FIG. 8B** shows a plot illustrating effect of arginine (in mM) on monomer content after four weeks at storage at 50°C. **FIG. 8C** shows a plot illustrating effect of arginine (in mM) on main charged peak (MP) species. **FIG. 8D** shows a plot illustrating effect of arginine (in mM)

on acidic charged species. Solid lines represent predicted values, and dashed lines represent upper and lower confidence intervals.

[050] **FIG. 9A** shows a plot illustrating effect of pH on viscosity attributes of felzartamab. **FIG. 9B** shows a plot illustrating effect of pH on monomer content after four weeks at storage at 50°C. **FIG. 9C** shows a plot illustrating effect of pH on main charged peak (MP) species **FIG. 9D** shows a plot illustrating effect of pH on acidic charged species. Solid lines represent predicted values, and dashed lines represent upper and lower confidence intervals.

[051] **FIG. 10A** shows a plot illustrating effect of trehalose concentration (from 90 to 240 mM) on viscosity attributes of felzartamab. **FIG. 10B** shows a plot illustrating effect of trehalose concentration (from 90 to 240 mM) on monomer content after four weeks at storage at 50°C. **FIG. 10C** shows a plot illustrating effect of trehalose concentration (from 90 to 240 mM) on main charged peak (MP) species. **FIG. 10D** shows a plot illustrating effect of trehalose concentration (from 90 to 240 mM) on acidic charged species. Solid lines represent predicted values, and dashed lines represent upper and lower confidence intervals.

[052] **FIG. 11A** shows a plot illustrating felzartamab monomer content as determined by UHP-SEC in formulations FC1 to FC6 stored up to 6 months at 5°C. **FIG. 11B** shows a plot illustrating felzartamab monomer content as determined by UHP-SEC in formulations FC1 to FC6 stored up to 6 months at 25°C/60% relative humidity. **FIG. 11C** shows a plot illustrating felzartamab monomer content as determined by UHP-SEC in formulations FC1 to FC6 stored up to 6 months at 40°C/75% relative humidity.

[053] **FIG. 12A** shows a bar graph illustrating micro-flow imaging results for particle size class $\geq 10 \mu\text{m}$ for formulations FC1 to FC6 stored at 25°C and 60% relative humidity for up to six months. **FIG. 12B** shows a bar graph illustrating micro-flow imaging results for particle size class $\geq 25 \mu\text{m}$ for formulations FC1 to FC6 stored at 25°C and 60% relative humidity for up to six months.

DETAILED DESCRIPTION

[054] Disclosed herein, in certain embodiments, are highly concentrated liquid formulations (HCLF) for an anti-CD38 antibody or antigen-binding portion thereof. The disclosed formulations are capable of maintaining the stability of the antibody over long periods of time and are suitable for subcutaneous administration to a subject (*e.g.*, a human). The HCLFs disclosed herein exhibit additional advantages in that they: (1) facilitate delivery of higher antibody doses in a smaller volume, (2) have physico-chemical characteristics that are favorable for syringeability and injection, and (3) do not require lyophilization and subsequent

reconstitution to maintain antibody stability and usability of the formulation over time, among others.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. Generally, nomenclatures utilized in connection with techniques described herein are those well-known and commonly used in the art. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[055] As used herein, singular forms “a,” “and,” and “the” include plural referents unless the context clearly indicates otherwise. Thus, *e.g.*, reference to “an antibody” includes a plurality of antibodies and reference to “an antibody” in certain embodiments, includes multiple antibodies, and so forth.

[056] As used herein, all numerical values or numerical ranges include whole integers within or encompassing such ranges and fractions of the values or the integers within or encompassing ranges unless the context clearly indicates otherwise. Thus, *e.g.*, reference to a range of 90-100% includes 91%, 92%, 93%, 94%, 95%, 95%, 97%, *etc.*, as well as 91.1%, 91.2%, 91.3%, 91.4%, 91.5%, *etc.*, 92.1%, 92.2%, 92.3%, 92.4%, 92.5%, *etc.*, and so forth. In another example, reference to a range of 1-5,000-fold includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20-fold, *etc.*, as well as 1.1, 1.2, 1.3, 1.4, 1.5-fold, *etc.*, 2.1, 2.2, 2.3, 2.4, 2.5-fold, *etc.*, and so forth.

[057] “About,” as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$ from a specified value, as such variations are appropriate to perform the disclosed methods.

[058] The term “antibody” as used herein refers to a protein which interacts with an antigen and comprises at least two heavy chains (HC) and two light chains (LC) inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. The heavy chain constant region of an IgG is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into hypervariable regions, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed

framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from N-terminus to C-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system. The term “antibody” includes for example, monoclonal antibodies, human antibodies, humanized antibodies, camelized antibodies and chimeric antibodies. The antibodies can be of any isotype (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. Both the light and heavy chains are divided into regions of structural and functional homology.

[059] As used herein, the term “antibody fragment” refers to one or more portions of an antibody that retain the ability to specifically interact (*e.g.*, by binding, steric hindrance, stabilizing spatial distribution) with an antigen. Examples of binding fragments include, but are not limited to, a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment, which consists of a VH domain; and an isolated CDR. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined using recombinant methods by a synthetic linker that allows them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv)). Such single chain antibodies are also intended to be encompassed within the term “antibody fragment.” These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antibody fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR, and bis-scFv. Antibody fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen-binding sites.

[060] As used herein, the terms “complementarity-determining regions,” “CDRs,” and “hypervariable regions” refer to the parts of the variable domains in antibodies that determine the antibodies' binding specificities to their specific antigen. A single variable region of an antibody polypeptide will typically comprise three CDRs, usually designated CDR1, CDR2, and CDR3.

More particularly, a heavy chain variable region may contain CDRs designated HCDR1, HCDR2, and HCDR3; likewise, light chain variable region may contain CDRs LCDR1, LCDR2, and LCDR3. Multiple methods may be used to define a CDR sequence. The current art utilizes various numbering schemes with different definitions of CDR lengths and positions. For example, IMGT numbering scheme is a standardized numbering system based on alignments of sequences from a complete reference gene database including the whole immunoglobulin superfamily. The Kabat numbering scheme is based on sequence alignment and uses “variability parameter” of a given amino acid position (the number of different amino acids at a given position divided by the frequency of the most occurring amino acid at that position) to predict CDRs. The Chothia numbering scheme, on the other hand, is a structure-based numbering scheme where antibody crystal structures are aligned as define the loop structures as CDRs. The Martin numbering scheme focuses on the structure alignment of different framework regions of unconventional lengths. Honneger’s numbering scheme (Aho’s) is based on structural alignments of the 3D structure of the variable regions and uses structurally conserved Ca positions to deduce framework and CDR lengths. One of skill in the art will note that the definition of a CDR will vary based on the method used. Accordingly, CDR sequences of a given heavy or light chain variable region may vary depending on the numbering system used. Any method of defining a CDR is contemplated with the sequences disclosed herein.

[061] As used herein, the term “monomer,” when referring to an antibody (*e.g.*, an anti-CD38 antibody, such as felzartamab), means a single and intact (*i.e.*, not fragmented) immunoglobulin molecule that is not part of an antibody aggregate. An antibody monomer can be identified in a complex mixture of antibody monomers and antibody aggregates (*e.g.*, low-molecular weight (LMW) and high-molecular weight (HMW) aggregates) using standard methods. For example, an antibody monomer can be identified in a complex mixture using liquid chromatographic techniques (*e.g.*, size exclusion chromatography (SEC), high-performance liquid chromatography (HPLC), ultra-high performance chromatography (UHPC), or combinations thereof). Typically, an antibody monomer measured using SEC typically has a molecular weight of about 150 kDa.

[062] The terms “pharmaceutical formulation,” “pharmaceutical composition,” or “formulation” refer to a preparation which is in such form as to permit the biological activity of an active pharmaceutical ingredient (API) contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation is administered. Such formulations are sterile. A “sterile” formulation is aseptic or free from all living microorganisms and their spores.

[063] As used herein, the terms “treatment,” “treating,” and the like, in some cases, refer to administering an agent, or carrying out a procedure, for the purposes of obtaining an effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or is therapeutic in terms of effecting a partial or complete cure for a disease and/or symptoms of the disease. “Treatment,” as used herein, includes treatment of a disease or disorder in a mammal, particularly in a human, and includes: (a) preventing the disease or a symptom of a disease from occurring in a subject which is predisposed to the disease but has not yet been diagnosed as having it (*e.g.*, including diseases that is associated with or caused by a primary disease; (b) inhibiting the disease, *i.e.*, arresting its development; and (c) relieving the disease, *i.e.*, causing regression of the disease. The term treating includes to any indicia of success in the treatment or amelioration or prevention of a disease or disorder, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disease condition more tolerable to the patient; slowing in the rate of degeneration or decline; or making the final point of degeneration less debilitating. The treatment or amelioration of symptoms is based on one or more objective or subjective parameters, including the results of an examination by a physician. Accordingly, the term “treating” includes the administration of the agents of the present disclosure to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with diseases. The term “therapeutic effect” refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or side effects of the disease in the subject. A subject is “treated” for a disease or disorder if, after receiving a therapeutic amount of an antibody of the present disclosure, the patient shows observable and/or measurable change in a parameter or symptom of the disease or disorder.

[064] As used herein, the term “stabilizer” refers to a component of a pharmaceutical formulation, such as a high concentration liquid antibody formulation disclosed herein, that maintains desirable properties of an active pharmaceutical ingredient, *e.g.*, a protein, such as an antibody, in the formulation until it is administered to a patient. For example, a stabilizer can be a sugar, sugar alcohol, amino acid(s), surfactant, buffer, or polymer that promotes longevity of the formulation. A stabilizer can also prevent degradation (*e.g.*, aggregation and precipitation) and/or chemical modification (*e.g.*, deamidation or oxidation) of the protein in the formulation over time and/or following multiple freeze-thaw cycles.

[065] As used herein, the phrase “visible proteinaceous particles” refers to protein aggregates that precipitate out of a liquid pharmaceutical formulation disclosed herein following protein degradation and/or aggregation resulting from stress (*e.g.*, heat stress), chemical modification, repeated freeze-thaw cycles, *etc.*

High Concentration Liquid Formulations

[066] Disclosed herein, in certain embodiments, are high concentration liquid formulations (HCLFs) containing an anti-CD38 antibody or antigen-binding fragment or equivalent thereof (*e.g.*, felzartamab or an antigen-binding fragment or equivalent thereof), a sugar, a non-ionic surfactant, a stabilizer, a histidine buffer, and having a pH within a desirable range. In certain embodiments, the disclosed liquid formulations are useful for subcutaneous or intramuscular administration to a subject (*e.g.*, a human).

Antibodies

[067] Disclosed herein are high concentration liquid formulations (HCLF) comprising an antibody or antigen-binding fragment or equivalent thereof. In certain embodiments, the antibody or antigen-binding fragment or equivalent thereof is a monoclonal antibody or antigen-binding fragment or equivalent thereof. In certain embodiments, the antibody or antigen-binding fragment or equivalent thereof specifically binds to CD38. CD38 (also known as ADP-ribosyl cyclase 1, cADPr hydrolase 1, Cyclic ADP-ribose hydrolase 1, and T10) is a type II transmembrane glycoprotein that synthesizes and hydrolyzes the second messenger, cyclic adenosine 5'-diphosphate-ribose (cADPr). CD38 can exist in soluble or membrane-bound form, and is, therefore, capable of mediating intracellular and extracellular signaling. Human CD38 (UniProt: P28907) has the amino acid sequence of SEQ ID NO: 9, shown below.

MANCEFSPVSGDKPCCRLSRRALCLGVSVLVLVAVVPRWRQQWSGPGTTKRF
 PETVLARCVKYTEIHPEMRHVDCQSVWDAFKGAFISKHPCNITEEDYQPLMKLGTQTVP
 CNKILLWSRIKDLAQFTQVQRDMFTLEDTLGLYADDLTWCGEFNTSKINYQSCPDW
 RKDCSNNPVSVFWKTVSRRFAEACDVVHVMLNGSRSKIFDKNSTFGSVEVHNLQPEK
 VQTLEAWVIHGGREDSRDLCQDPTIKELESIISKRNIFSCKNYRPDKFLQCVKNPEDSS
 CTSEI

(SEQ ID NO: 9)

[068] In certain embodiments, an anti-CD38 antibody disclosed herein or an antigen-binding fragment or equivalent thereof is monoclonal. In certain embodiments, the monoclonal or antigen-binding fragment thereof is a mouse, chimeric, humanized, or human or antigen-binding fragment thereof. In certain embodiments, the monoclonal or antigen-binding fragment thereof is a human or antigen-binding fragment thereof. In certain embodiments, the monoclonal or

antigen-binding fragment thereof is a humanized or antigen-binding fragment thereof. In certain embodiments, the monoclonal or antigen-binding fragment thereof is a chimeric or antigen-binding fragment thereof. In certain embodiments, the monoclonal or antigen-binding fragment thereof is a mouse or antigen-binding fragment thereof.

[069] In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 or antigen-binding fragment thereof at a concentration of at least 100 mg/mL (*e.g.*, at least 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 mg/mL, or more). In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 antibody or antigen-binding fragment or equivalent thereof at a concentration of 100-200 mg/mL. In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 antibody or antigen-binding fragment or equivalent thereof at a concentration of 100-175 mg/mL. In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 antibody or antigen-binding fragment or equivalent thereof at a concentration of 100-150 mg/mL. In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 antibody or antigen-binding fragment or equivalent thereof at a concentration of about 150 mg/mL. In certain embodiments, a pharmaceutical formulation of the present disclosure comprises an anti-CD38 antibody or antigen-binding fragment or equivalent thereof at a concentration of 150 mg/mL.

[070] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more amino acid sequences disclosed in Table 1. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) amino acid sequences disclosed in Table 2. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more amino acid sequences disclosed in Table 3. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more amino acid sequences disclosed in Table 4. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more amino acid sequences disclosed in Table 5. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises one or more amino acid sequences disclosed in Table 6.

[071] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 1, HCDR2 of SEQ

ID NO: 2, HCDR3 of SEQ ID NO: 3, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 4, LCDR2 of SEQ ID NO: 5, and LCDR3 of SEQ ID NO: 6. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 7 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 8. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 7 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 8. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 7 and a VL comprising an amino acid sequence of SEQ ID NO: 8. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH having 100% sequence identity to the amino acid sequence of SEQ ID NO: 7 and a VL having 100% sequence identity to the amino acid sequence of SEQ ID NO: 8. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a heavy chain (HC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a light chain (LC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or

equivalent thereof comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 13. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 13.

[072] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is felzartamab or a biosimilar thereof. Felzartamab (also known as HIB202, MOR202, MOR03087, and MOR3087) is a monoclonal anti-CD38 antibody that has been shown to have proven clinical efficacy in the treatment of certain cancers and autoimmune indications. Felzartamab is capable of selectively depleting CD38-positive plasmablasts and plasma cells via antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP) independent of complement-dependent cytotoxicity (CDC), which has been shown to be associated with adverse infusion-related reactions observed with other anti-CD38 antibodies. The amino acid sequences of felzartamab are provided in Table 1, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to Kabat numbering system. Felzartamab also includes an Fc region.

Table 1: Felzartamab sequences

Domain	Sequence	SEQ ID NO
HCDR1	SYYMN	1
HCDR2	GISGDPSNTYYADSVKG	2
HCDR3	DLPLVYTGfAY	3
LCDR1	SGDNLRHYYVY	4

LCDR2	GDSKRPS	5
LCDR3	QTYTGGASL	6
VH amino acid sequence	QVQLVESGGGLVQPGGSLRLSCAASG FTFSSYYMNWVRQAPGKGLEWVSGIS GDPSNTYYADSVKGRFTISRDN SKNT LYLQMNSLRAEDTAVYYCARDLPLV YTGFAYWGQGTLVTVSS	7
VL amino acid sequence	DIELTQPPSVSVAPGQTARISCSGDNL RHYYVYWYQQKPGQAPVLVIYGDSK RPSGIPERFSGSNSGNTATLTISGTQAE DEADYYCQTYTGGASLVFGGGTKLT VLGQ	8
VH nucleic acid sequence	CAGGTGCAATTGGTGGAAAGCGGCG GCGGCCTGGTGCAACCGGGCGGCAG CCTGCGTCTGAGCTGCGCGGCCTCC GGATTTACCTTTTCTTCTTATTATAT GAATTGGGTGCGCCAAGCCCCTGGG AAGGGTCTCGAGTGGGTGAGCGGTA TCTCTGGTGATCCTAGCAATACCTAT TATGCGGATAGCGTGAAAGGCCGTT TTACCATTTCACGTGATAATTGAA AAACACCCTGTATCTGCAAATGAAC AGCCTGCGTGCGGAAGATACGGCCG TGTATTATTGCGCGCGTGATCTTCCT CTTGTTTATACTGGTTTTGCTTATTG GGGCAAGGCACCCTGGTGACGGTT AGCTCA	10
VL nucleic acid sequence	GATATCGAACTGACCCAGCCGCCTT CAGTGAGCGTTGCACCAGGTCAGAC CGCGCGTATCTCGTGTAGCGGCGAT AATCTTCGTCATTATTATGTTTATTG GTACCAGCAGAAACCCGGGCAGGC GCCAGTTCTTGTGATTTATGGTGATT	11

	CTAAGCGTCCCTCAGGCATCCCGGA ACGCTTTAGCGGATCCAACAGCGGC AACACCGCGACCCTGACCATTAGCG GCACTCAGGCGGAAGACGAAGCGG ATTATTATTGCCAGACTTATACTGGT GGTGCTTCTCTTGTGTTTGGCGGCGG CACGAAGTTAACCGTTCTTGGCCAG	
Heavy chain amino acid sequence	QVQLVESGGGLVQPGGSLRLSCAASGF TFSSYYMNWVRQAPGKGLEWVSGISG DPSNTYYADSVKGRFTISRDN SKNTLYL QMNSLRAEDTAVYYCARDLPLVYTG AYWGQGLTVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYCNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKV NKALPAPIEKTISKAKGQPREPQVYTL PSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	12
Light chain amino acid sequence	DIELTQPPSVSVAPGQTARISCSGDNLR HYVYVYWYQQKPGQAPVLIYGDSKRP SGIPERFSGSNSGNTATLTISGTAEDEA DYVCQTYTGASLVFGGGTKLTVLGQP KAAPSVTLFPPSSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTP SKQSNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS	13

[073] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a

heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 14, HCDR2 of SEQ ID NO: 15, HCDR3 of SEQ ID NO: 16, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 17, LCDR2 of SEQ ID NO: 18, and LCDR3 of SEQ ID NO: 19. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence of SEQ ID NO: 21. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH having 100% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL having 100% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a heavy chain (HC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a light chain (LC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino

acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 23.

[074] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is isatuximab or a biosimilar thereof. Isatuximab (also known as anti-CD38 monoclonal antibody – Sanofi, hu38SB19, isatuximab-irfc, SAR-650984, and Sarclisa) is a monoclonal anti-CD38 antibody that has been shown to have proven clinical efficacy in the treatment of certain cancers and autoimmune indications. The amino acid sequences of isatuximab are provided in Table 2, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to Kabat numbering system. Isatuximab also includes an Fc region.

Table 2: Isatuximab sequences

Domain	Sequence	SEQ ID NO
HCDR1	DYWMQ	14
HCDR2	TIYPGDGDTGYAQKFQG	15
HCDR3	GDYYGSNSLDY	16
LCDR1	KASQDVSTVVA	17
LCDR2	SASYRYI	18

LCDR3	QQHYSPPYT	19
VH amino acid sequence	QVQLVQSGAEVAKPGTSVKLSCKASG YTFTDYWMQWVKQRPGQGLEWIGTI YPGDGDTGYAQKFQGKATLTADKSS KTVYMHLSLASEDSAVYYCARGDY YGSNSLDYWGQGTSVTVSS	20
VL amino acid sequence	DIVMTQSHLSMSTSLGDPVSITCKASQ DVSTVVAWYQQKPGQSPRRLIYSASY RYIGVPDRFTGSGAGTDFTFTISSVQA EDLAVYYCQQHYSPPYTFGGGTKLEI KR	21
Heavy chain amino acid sequence	QVQLVQSGAEVAKPGTSVKLSCKASG YTFTDYWMQWVKQRPGQGLEWIGTI YPGDGDTGYAQKFQGKATLTADKSS KTVYMHLSLASEDSAVYYCARGDY YGSNSLDYWGQGTSVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCP APPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSGDSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	22
Light chain amino acid sequence	DIVMTQSHLSMSTSLGDPVSITCKASQ DVSTVVAWYQQKPGQSPRRLIYSASY RYIGVPDRFTGSGAGTDFTFTISSVQA EDLAVYYCQQHYSPPYTFGGGTKLEI	23

	KRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNR GEC	
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[075] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 24, HCDR2 of SEQ ID NO: 25, HCDR3 of SEQ ID NO: 26, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 27, LCDR2 of SEQ ID NO: 28, and LCDR3 of SEQ ID NO: 29. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence of SEQ ID NO: 31. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH having 100% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL having 100% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a heavy chain (HC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a light chain (LC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid

sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 33.

[076] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is daratumumab or a biosimilar thereof. Daratumumab (also known as Dalinivi, Dara-IV, Darasarex, Darzalex, Darxalex SC, HuMax-CD38, and JNJ-54767414) is a monoclonal anti-CD38 antibody that has been shown to have proven clinical efficacy in the treatment of certain cancers. The amino acid sequences of daratumumab are provided in Table 3, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to definitions provided in WO 2015/130728 and WO 2015/130732. Daratumumab also includes an Fc region.

Table 3: Daratumumab sequences

Domain	Sequence	SEQ ID NO
HCDR1	SFAMS	24
HCDR2	AISGSGGGTTYADSVK	25
HCDR3	DKILWFGEPVFDY	26
LCDR1	RASQSVSSYLA	27
LCDR2	DASNRAT	28
LCDR3	QQRSNWPPTF	29
VH amino acid sequence	EVQLLESGGGLVQPGGSLRLSCAVSG FTFNSFAMSWVRQAPGKGLEWVSAIS GSGGGTTYADSVKGRFTISRDN SKNT LYLQMNSLRAEDTAVYFCAKDILW FGEPVFDYWGQGT LTVSS	30
VL amino acid sequence	EIVLTQSPATLSLSPGERATLSCRASQS VSSYLAWYQQKPGQAPRLLIYDASNR ATGIPARFSGSGSGTDFTLTIS SLEPED FAVYYCQQRSNWPPTFGQG TKVEIK	31
Heavy chain amino acid sequence	EVQLLESGGGLVQPGGSLRLSCAVSG FTFNSFAMSWVRQAPGKGLEWVSAIS GSGGGTTYADSVKGRFTISRDN SKNT LYLQMNSLRAEDTAVYFCAKDILW FGEPVFDYWGQGT LTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKRVEPKSCDKTHTCPPCP APELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTTPVLDSDGSFFLYSKLTVD	32

	KSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	
Light chain amino acid sequence	EIVLTQSPATLSLSPGERATLSCRASQS VSSYLAWYQQKPGQAPRLLIYDASNR ATGIPARFSGSGSGTDFTLTSSLEPED FAVYYCQQRSNWPPTFGQGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKSTYLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C	33

[077] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 34, HCDR2 of SEQ ID NO: 35, HCDR3 of SEQ ID NO: 36, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 37, LCDR2 of SEQ ID NO: 38, and LCDR3 of SEQ ID NO: 39. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence of SEQ ID NO: 41. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a

VH having 100% sequence identity to the an amino acid sequence of SEQ ID NO: 40 and a VL having 100% sequence identity to the an amino acid sequence of SEQ ID NO: 41. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a heavy chain (HC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a light chain (LC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 43.

[078] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is mezagitamab or a biosimilar thereof. Mezagitamab (also known as anti-CD38 mAb, TAK-079, TAK 079, TAK079, and AB79) is a monoclonal anti-CD38 antibody that has

been shown to have proven clinical efficacy in the treatment of certain cancers and autoimmune indications. The amino acid sequences of mezagitamab are provided in Table 4, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to definitions provided in WO 2012/092612. Mezagitamab also includes an Fc region.

Table 4: Mezagitamab sequences

Domain	Sequence	SEQ ID NO
HCDR1	GFTFDDYG	34
HCDR2	ISWNGGKT	35
HCDR3	AAGSLFHDSSGFYFGH	36
LCDR1	SSNIGDNY	37
LCDR2	RDS	38
LCDR3	QSYDSSLGS	39
VH amino acid sequence	EVQLLESGGGLVQPGGSLRLSCAASG FTFDDYGMSWVRQAPGKGLEWVSDI SWNGGKTHYVDSVKGQFTISRDN SK NTLYLQMNSLRAEDTAVYYCARGSL FHDSSGFYFGHWGQGT LVT VSSASTK GPSVFPLA	40
VL amino acid sequence	QSVLTQPPSASGTPGQRVTISCSGSSSN IGDNYVSWYQQLPGTAPKLLIYRDSQ RPSGVPDRFSGSKSGTSASLAISGLRSE DEADYYCQSYDSSLGSVFGGG TKLT VLGQPKANPTVTLFPPSSEEL	41
Heavy chain amino acid sequence	EVQLLESGGGLVQPGGSLRLSCAASG FTFDDYGMSWVRQAPGKGLEWVSDI SWNGGKTHYVDSVKGQFTISRDN SK NTLYLQMNSLRAEDTAVYYCARGSL FHDSSGFYFGHWGQGT LVT VSSASTK GPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVT VSWNSGALTSGVHTFPAVL QSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDRVEPKSCDKTHTCP	42

	PCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFCFSVMHEALHN HYTQKSLSLSPGK	
Light chain amino acid sequence	QSVLTQPPSASGTPGQRTISCSGSSSN IGDNYVSWYQQLPGTAPKLLIYRDSQ RPSGVPDRFSGSKSGTSASLAISGLRSE DEADYYCQSYDSSLSGSVFGGGTCLT VLGQPKANPTVTLFPPSSEELQANKAT LVCLISDFYPGAVTVAWKADGSPVKA GVETTKPSKQSNKYAASSYLSLTPE QWKSHRSYSCQVTHEGSTVEKTVAPT ECS	43

[079] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 44, HCDR2 of SEQ ID NO: 45, HCDR3 of SEQ ID NO: 46, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 47, LCDR2 of SEQ ID NO: 48, and LCDR3 of SEQ ID NO: 49. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent

thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence of SEQ ID NO: 51. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH having 100% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL having 100% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a heavy chain (HC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a light chain (LC) comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, an

anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 53.

[080] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is erzotabart or a biosimilar thereof. Erzotabart (also known as anti-CD38 Monoclonal Antibody GEN3014, GEN 3014, GEN-3014, GEN3014, and HexaBody-CD38) is a monoclonal anti-CD38 antibody that has been shown to have proven clinical efficacy in the treatment of certain cancers. The amino acid sequences of erzotabart are provided in Table 5, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to Kabat numbering system. Erzotabart also includes an Fc region.

Table 5: Erzotabart sequences

Domain	Sequence	SEQ ID NO
HCDR1	SYAIS	44
HCDR2	RIIRFLGIANYAQKFQG	45
HCDR3	EPGERDPDAVDI	46
LCDR1	RASQGIRSWLA	47
LCDR2	AASSLQS	48
LCDR3	QQYNSYPLT	49
VH amino acid sequence	QVQLVQSGAEVKKPGSSVKVSCKAF GGTFSSYAISWVRQAPGQGLEWMGRI IRFLGIANYAQKFQGRVTLIADKSTNT AYMELSSLRSEDTAVYYCAGEPGERD PDAVDIWGQGTMVTVSS	50
VL amino acid sequence	DIQMTQSPSSLSASVGDRVTITCRASQ GIRSWLAWYQQKPEKAPKSLIYAASS LQSGVPSRFSGSGSGTDFTLTISLQPE DFATYYCQQYNSYPLTFGGGTKVEIK RTV	51
Heavy chain amino acid sequence	QVQLVQSGAEVKKPGSSVKVSCKAF GGTFSSYAISWVRQAPGQGLEWMGRI IRFLGIANYAQKFQGRVTLIADKSTNT	52

	AYMESSLRSEDTAVYYCAGEPGERD PDAVDIWGQGTMTVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKRVEPKSCDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTTPVLDSGDSFFLYSKLTVD KSRWQQGNVFCFSVMHGALHNHYTQ KSLSLSPGK	
Light chain amino acid sequence	DIQMTQSPSSLSASVGDRTITCRASQ GIRSWLAWYQQKPEKAPKSLIYAASS LQSGVPSRFSGSGSGTDFTLTISLQPE DFATYYCQQYNSYPLTFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVC LLNFPYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRG EC	53

[081] In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a variable heavy chain region (VH) comprising a heavy chain complementarity determining region 1 (HCDR1) of SEQ ID NO: 54, HCDR2 of SEQ ID NO: 55, HCDR3 of SEQ ID NO: 56, and a variable light chain region (VL) comprising a light chain complementarity determining region 1 (LCDR1) of SEQ ID NO: 57, LCDR2 of SEQ ID NO: 58, and LCDR3 of SEQ ID NO: 59. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 60 and a VL comprising an amino acid sequence having at least 85%

sequence identity to the amino acid sequence of SEQ ID NO: 61. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 60 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 61. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 60 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 61. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH comprising an amino acid sequence of SEQ ID NO: 60 and a VL comprising an amino acid sequence of SEQ ID NO: 61. In certain embodiments, an anti-CD38 antibody disclosed herein or antigen-binding fragment or equivalent thereof comprises a VH having 100% sequence identity to the amino acid sequence of SEQ ID NO: 60 and a VL having 100% sequence identity to the amino acid sequence of SEQ ID NO: 61.

[082] In certain embodiments, the monoclonal antibody suitable for use with the HCLFs disclosed herein is STI-6129 or fragment, portion, or a biosimilar thereof. STI-6129 (also known as STI 6129, STI6129, LNDS1001, CD38-077, ADC STI-6129, Anti-CD38 ADC STI-6129, and Anti-CD38-Duostatin 5.2 ADC STI-6129) is an antibody drug-conjugate (ADC) composed of STI-5171, a fully monoclonal anti-CD38 antibody, site-specifically conjugated, via a non-polyethylene glycol linker, to a monomethyl auristatin F (MMAF)-derived cytotoxic payload, with potential antineoplastic activity. In certain embodiments, the antibody disclosed herein is the STI-5171 antibody portion of STI-6129 without the drug conjugate moiety. The amino acid sequences of STI-6129 are provided in Table 6, below. Unless stated otherwise, all complementarity determining regions (CDRs) are defined according to Kabat numbering system. STI-6129 also includes an Fc region.

Table 6: STI-6129 sequences

Domain	Sequence	SEQ ID NO
HCDR1	DDYMS	54
HCDR2	SVSNGRPTTTYADSVRG	55
HCDR3	EDWGGEFTD	56
LCDR1	SGSSSNIGINFVY	57

LCDR2	KNNQRPS	58
LCDR3	AAWDDSLSGYV	59
VH amino acid sequence	QVQLVESGGGLVKPGGSLRLSCAASG FTFSDDYMSWIRQAPGKGLEWVASVS NGRPTTTYADSVRGRFTISRDNKNS LYLQMNSLRAEDTAVYYCAREDWGG EFTDWGRGTLVTVSS	60
VL amino acid sequence	QSVLTQPPSASGTSGQRVTISCSGSSSN IGINFVYWYQHLPGTAPKLLIYKNNQ RPSGVPDRFSGSKSGNSASLAISGLRS EDEADYYCAAWDDSLSGYVFGSGTK VTVL	61

Binding Agents

[083] Disclosed herein, in certain embodiments, are pharmaceutical compositions comprising a binding agent comprising a means for binding to one or more (*e.g.*, 1, 2, or more) epitopes of a CD38 protein, *e.g.*, a human CD38 protein, such as a wild-type human CD38 protein or a variant thereof. In certain embodiments, the means for binding to one or more epitopes of a CD38 protein is a binding agent that specifically binds to a CD38 protein (*e.g.*, a human CD38 protein). In certain embodiments, the binding agent is an antibody or an antigen-binding fragment or equivalent thereof. In certain embodiments, the antibody or antigen-binding fragment or equivalent thereof is specific to a CD38 protein, such as a human CD38 protein.

[084] In certain embodiments, a binding agent disclosed herein comprises one or more amino acid sequences disclosed in Table 1. In certain embodiments, a binding agent disclosed herein comprises one or more (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) amino acid sequences disclosed in Table 2. In certain embodiments, binding agent disclosed herein comprises one or more amino acid sequences disclosed in Table 3. In certain embodiments, a binding agent disclosed herein comprises one or more amino acid sequences disclosed in Table 4. In certain embodiments, a binding agent disclosed herein comprises one or more amino acid sequences disclosed in Table 5. In certain embodiments, a binding agent disclosed herein comprises one or more amino acid sequences disclosed in Table 6.

[085] In certain embodiments, the binding agent comprises a VH comprising a HCDR1 of SEQ ID NO: 1, HCDR2 of SEQ ID NO: 2, HCDR3 of SEQ ID NO: 3, and a VL comprising a LCDR1 of SEQ ID NO: 4, LCDR2 of SEQ ID NO: 5, and LCDR3 of SEQ ID NO: 6. In certain

[illegible]

having 100% sequence identity to the amino acid sequence of SEQ ID NO: 12 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 13.

[086] In certain embodiments, the binding agent is an antibody or an antigen-binding fragment or equivalent thereof. In certain embodiments, the binding agent comprises a VH comprising a HCDR1 of SEQ ID NO: 14, HCDR2 of SEQ ID NO: 15, HCDR3 of SEQ ID NO: 16, and a VL comprising a LCDR1 of SEQ ID NO: 17, LCDR2 of SEQ ID NO: 18, and LCDR3 of SEQ ID NO: 19. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 20 and a VL comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 21. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent

comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 23. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 22 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 23.

[087] In certain embodiments, the binding agent is an antibody or an antigen-binding fragment or equivalent thereof. In certain embodiments, the binding agent comprises a VH comprising a HCDR1 of SEQ ID NO: 24, HCDR2 of SEQ ID NO: 25, HCDR3 of SEQ ID NO: 26, and a VL comprising a LCDR1 of SEQ ID NO: 27, LCDR2 of SEQ ID NO: 28, and LCDR3 of SEQ ID NO: 29. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a VL comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 31. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain

embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 33. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 32 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 33.

[088] In certain embodiments, the binding agent is an antibody or an antigen-binding fragment or equivalent thereof. In certain embodiments, the binding agent comprises a VH comprising a HCDR1 of SEQ ID NO: 34, HCDR2 of SEQ ID NO: 35, HCDR3 of SEQ ID NO: 36, and a VL comprising a LCDR1 of SEQ ID NO: 37, LCDR2 of SEQ ID NO: 38, and LCDR3 of SEQ ID NO: 39. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 41. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 40 and a VL comprising an amino acid sequence having 100% sequence identity to the amino acid sequence

of SEQ ID NO: 41. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 43. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 42 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 43.

[089] In certain embodiments, the binding agent is an antibody or an antigen-binding fragment or equivalent thereof. In certain embodiments, the binding agent comprises a VH comprising a HCDR1 of SEQ ID NO: 44, HCDR2 of SEQ ID NO: 45, HCDR3 of SEQ ID NO: 46, and a VL comprising a LCDR1 of SEQ ID NO: 47, LCDR2 of SEQ ID NO: 48, and LCDR3 of SEQ ID NO: 49. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 90%

sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, the binding agent comprises a VH comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a VL comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 51. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 75% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 80% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 53. In certain embodiments, the binding agent comprises a HC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 52 and a LC comprising an amino acid sequence having 100% sequence identity to the amino acid sequence of SEQ ID NO: 53.

Sugars

[090] In certain embodiments, the pharmaceutical formulations disclosed herein comprise a sugar. Without wishing to be bound by any theory, sugars added as excipients to pharmaceutical formulations containing proteins, such as antibodies, may act as stabilizers, lyoprotectants, and/or bulking agents in solid form. Generally, it is believed that sugars stabilize the native state conformation of proteins by increasing the free energy associated with protein unfolding. Furthermore, sugars help prevent interactions between antibodies and solvents.

[091] In certain embodiments, the sugar is selected from trehalose, sucrose, raffinose, maltose, lactose, mannitol, glycerol, and sorbitol. In certain embodiments, the pharmaceutical formulation comprises the sugar at a concentration of about 240 mM to about 260 mM (*e.g.*, 220 to 280 mM). In certain embodiments, the pharmaceutical formulation comprises the sugar at a concentration of about 240 mM (*e.g.*, between 220 and 260 mM). In certain embodiments, the pharmaceutical formulation comprises the sugar at a concentration of 240 mM. In certain embodiments, the pharmaceutical formulation comprises the sugar at a concentration of about 260 mM (*e.g.*, between 240 and 280 mM). In certain embodiments, the pharmaceutical formulation comprises the sugar at a concentration of 260 mM. In certain embodiments, a pharmaceutical formulation disclosed herein comprises trehalose. In certain embodiments, the pharmaceutical formulation comprises about 240 mM trehalose. In certain embodiments, the pharmaceutical formulation comprises 240 mM trehalose. In certain embodiments, a pharmaceutical formulation disclosed herein comprises sucrose. In certain embodiments, the pharmaceutical formulation comprises about 260 mM sucrose. In certain embodiments, the pharmaceutical formulation comprises 260 mM sucrose.

Non-ionic surfactants

[092] In certain embodiments, the pharmaceutical formulation according to the present disclosure comprises a non-ionic surfactant. Surfactants are generally chemical agents that reduce the surface tension or interfacial tension between two liquids, liquid and a gas, or liquid and a solid. Due to the amphiphilic nature of proteins, including antibodies, they may be subjected to substantial interfacial stress, *e.g.*, stress resulting from air/water interfaces during mixing of liquid formulations, ice/water interfaces during freezing/thawing, oil/water interfaces of transmembrane proteins, and the like. Without wishing to be bound by any theory, non-ionic surfactants added as excipients to pharmaceutical formulations containing proteins, such as

antibodies, may act to increase protein stability by minimizing adsorption to surfaces and interface-induced aggregation.

[093] Examples of non-ionic surfactants suitable for use with the pharmaceutical formulations disclosed herein, include, but are not limited to, polyoxyethylensorbitan fatty acid esters (*e.g.*, polysorbate 20 and polysorbate 80), polyethylene-polypropylene copolymers, polyethylene-polypropylene glycols, polyox ethylene-stearates, polyoxyethylene alkyl ethers, *e.g.*, polyoxyethylene monolauryl ether, alkylphenylpolyoxyethylene ethers (Triton-X), polyoxyethylene-polyoxypropylene copolymer (Poloxamer, Pluronic), sodium dodecyl sulphate (SDS).

[094] In certain embodiments, the non-ionic surfactant is polysorbate 20 or polysorbate 80. In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.01 to 0.5% (v/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.1% (v/v). In certain embodiments, the non-ionic surfactant is polysorbate 20. In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is about 0.1% (v/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is 0.1% (v/v). In certain embodiments, the non-ionic surfactant is poloxamer 188. In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.1 to 1.0% (v/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.5% (v/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is 0.5% (v/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.01 to 0.5% (w/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is 0.1% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.1 to 1.0% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.5% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is 0.5% (w/v).

[095] In certain embodiments, the non-ionic surfactant is polysorbate 20 or polysorbate 80. In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.01 to 0.5% (w/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain

embodiments, the non-ionic surfactant is polysorbate 20. In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is 0.1% (w/v). In certain embodiments, the non-ionic surfactant is poloxamer 188. In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.1 to 1.0% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.5% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is 0.5% (w/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.01 to 0.5% (w/v). In certain embodiments, the polysorbate 20 or polysorbate 80 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is about 0.1% (w/v). In certain embodiments, the polysorbate 20 concentration in the pharmaceutical formulation is 0.1% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.1 to 1.0% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is about 0.5% (w/v). In certain embodiments, the poloxamer 188 concentration in the pharmaceutical formulation is 0.5% (w/v).

Stabilizers

[096] In certain embodiments, the pharmaceutical formulation according to the present disclosure comprises a stabilizer. Generally, a stabilizer is any agent that promotes longevity of the active pharmaceutical ingredient (API) of a pharmaceutical formulation. In the context of a protein API (*e.g.*, an antibody, such as an anti-CD38 antibody), a stabilizer can be included to a pharmaceutical formulation to prevent degradation (*e.g.*, aggregation and precipitation) and/or chemical modification (*e.g.*, deamidation or oxidation) of the protein over time and/or following physical stress (*e.g.*, mixing, repeated freeze-thaw cycles, lyophilization, *etc.*).

[097] Stabilizers disclosed herein may include, but are not limited to proteins, *e.g.*, human serum albumin (HAS), bovine serum albumin (BSA), α -casein, globulins, α -lactalbumin, LDH, lysozyme, myoglobin, ovalbumin, and RNase A. In certain embodiments, stabilizers of the disclosure may include amino acids and their metabolites, such as glycine, alanine (α -alanine or β -alanine), arginine, betaine, leucine, lysine, glutamic acid, aspartic acid, methionine, proline, 4-hydroxyproline, sarcosine, γ -aminobutyric acid (GABA), opines (alanopine, octopine, or strombine), and trimethylamine N-oxide (TMAO). In certain embodiments, the stabilizer is methionine. In certain embodiments, the methionine is included in a pharmaceutical formulation

of the disclosure at a concentration of about 1 to 20 mM. In certain embodiments, methionine is included in a pharmaceutical formulation of the disclosure at a concentration of about 10 mM. In certain embodiments, methionine is included in a pharmaceutical formulation of the disclosure at a concentration of 10 mM.

Histidine buffer

[098] In certain embodiments, a pharmaceutical formulation of the present disclosure includes a histidine buffer. In certain embodiments, the histidine buffer is included in a pharmaceutical formulation of the disclosure at a concentration of about 10 mM. In certain embodiments, the histidine buffer is included in a pharmaceutical formulation of the disclosure at a concentration of 10 mM. In certain embodiments, the histidine buffer is histidine hydrochloride (His/HCl). In certain embodiments, the histidine buffer has a pH of about 5.5 to about 6.5. In certain embodiments, the histidine buffer has a pH of about 5.5. In certain embodiments, the histidine buffer has a pH of 5.5. In certain embodiments, the histidine buffer has a pH of about 6.0. In certain embodiments, the histidine buffer has a pH of 6.0.

Representative Embodiments

[099] In certain embodiments, the present disclosure provides a pharmaceutical formulation comprising:

- a) about 100 to 250 mg/mL of an antigen-binding protein (*e.g.*, an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof);
- b) about 5 to about 15 mM of a buffering agent (*e.g.*, a histidine buffer) having a pH of about 5.5 to about 6.5;
- c) about 200 to about 300 mM of a sugar (*e.g.*, sucrose or trehalose); and
- d) about 0.1% (v/v) to about 1% (v/v) of a non-ionic surfactant (*e.g.*, polysorbate 20 or poloxamer 188).

[0100] In certain embodiments, the present disclosure provides a pharmaceutical formulation comprising:

- a) about 100 to 250 mg/mL of an antigen-binding protein (*e.g.*, an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof);
- b) about 5 to about 15 mM of a buffering agent (*e.g.*, a histidine buffer) having a pH of about 5.5 to about 6.5;
- c) about 200 to 300 mM of a sugar (*e.g.*, sucrose or trehalose);
- d) about 5 to 20 mM of a stabilizer (*e.g.*, methionine); and

- e) about 0.1% (v/v) to 1% (v/v) of a non-ionic surfactant (*e.g.*, polysorbate 20 or poloxamer 188).

[0101] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8
- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt,
- c) about 200 mM to about 300 mM of trehalose;
- d) about 0.1% (v/v) to about 1.0% (v/v) of poloxamer 188;
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0102] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 200 mM to about 300 mM of sucrose;
- d) about 0.075% (v/v) to about 0.2% (v/v) of polysorbate 20 (PS20);
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0103] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a light chain complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 200 mM to about 300 mM of trehalose;
- d) about 0.075% (v/v) to about 0.2% (v/v) of PS20;
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0104] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.1% (v/v) of PS20; and
- e) a pH of about 5.5.

[0105] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.1% (v/v) PS20; and
- e) a pH of 5.5.

[0106] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.1% (v/v) PS20; and
- e) a pH of 5.5.

[0107] In certain embodiments, provided herein is a stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.1% (v/v) of PS20;
- e) about 10 mM of methionine; and
- f) a pH of about 5.5.

[0108] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;
- e) 0.1% (v/v) PS20; and
- f) a pH of 5.5.

[0109] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 240 mM trehalose;
- c) 10 mM methionine;

- d) 0.1% (v/v) PS20; and
- e) a pH of 5.5.

[0110] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.5% (v/v) of poloxamer 188; and
- e) a pH of about 5.5.

[0111] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.5% (v/v) poloxamer 188; and
- e) a pH of 5.5.

[0112] In certain embodiments, the stable liquid pharmaceutical formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202) ;
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.5% (v/v) poloxamer 188; and
- e) a pH of 5.5.

[0113] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino

acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;

- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.5% (v/v) of poloxamer 188;
- e) about 10 mM of methionine; and
- f) a pH of about 5.5.

[0114] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;
- e) 0.5% (v/v) poloxamer 188; and
- f) a pH of 5.5.

[0115] In certain embodiments, the stable liquid pharmaceutical formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202) ;
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;
- e) 0.5% (v/v) poloxamer 188; and
- f) a pH of 5.5.

[0116] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 260 mM of sucrose;
- d) about 0.1% (v/v) of PS20; and

- e) a pH of about 6.0.

[0117] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 0.1% (v/v) PS20; and
- d) a pH of 6.0.

[0118] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 0.1% (v/v) PS20; and
- d) a pH of 6.0.

[0119] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 260 mM of sucrose;
- d) about 0.1% (v/v) of PS20;
- e) about 10 mM of methionine; and
- f) a pH of about 6.0.

[0120] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 10 mM methionine;
- d) 0.1% (v/v) PS20; and
- e) a pH of 6.0.

[0121] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 10 mM methionine;
- d) 0.1% (v/v) PS20; and
- e) a pH of 6.0.

[0122] In certain embodiments, the present disclosure provides a pharmaceutical formulation comprising:

- a) about 100 to 250 mg/mL of an antigen-binding protein (*e.g.*, an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof);
- b) about 5 to about 15 mM of a buffering agent (*e.g.*, a histidine buffer) having a pH of about 5.5 to about 6.5;
- c) about 200 to about 300 mM of a sugar (*e.g.*, sucrose or trehalose); and
- d) about 0.1% (w/v) to about 1% (w/v) of a non-ionic surfactant (*e.g.*, polysorbate 20 or poloxamer 188).

[0123] In certain embodiments, the present disclosure provides a pharmaceutical formulation comprising:

- a) about 100 to 250 mg/mL of an antigen-binding protein (*e.g.*, an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof);
- b) about 5 to about 15 mM of a buffering agent (*e.g.*, a histidine buffer) having a pH of about 5.5 to about 6.5;
- c) about 200 to 300 mM of a sugar (*e.g.*, sucrose or trehalose);
- d) about 5 to 20 mM of a stabilizer (*e.g.*, methionine); and
- e) about 0.1% (w/v) to 1% (w/v) of a non-ionic surfactant (*e.g.*, polysorbate 20 or poloxamer 188).

[0124] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a

LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8

- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt,
- c) about 200 mM to about 300 mM of trehalose;
- d) about 0.1% (w/v) to about 1.0% (w/v) of poloxamer 188;
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0125] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 200 mM to about 300 mM of sucrose;
- d) about 0.075% (w/v) to about 0.2% (w/v) of polysorbate 20 (PS20);
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0126] In certain embodiments, provided herein is a stable liquid pharmaceutical composition comprising:

- a) about 144 mg/mL to about 176 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a light chain complementarity determining region 1 (LCDR1) amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;

- b) about 5 mM to about 50 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 200 mM to about 300 mM of trehalose;
- d) about 0.075% (w/v) to about 0.2% (w/v) of polysorbate 20 (PS20);
- e) about 5 mM to about 20 mM of methionine; and
- f) a pH from about 5.0 to about 6.5.

[0127] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.1% (w/v) of PS20; and
- e) a pH of about 5.5.

[0128] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.1% (w/v) PS20; and
- e) a pH of 5.5.

[0129] In certain embodiments, provided herein is a stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of

SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;

- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.1% (w/v) of PS20;
- e) about 10 mM of methionine; and
- f) a pH of about 5.5.

[0130] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;
- e) 0.1% (w/v) PS20; and
- f) a pH of 5.5.

[0131] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 240 mM trehalose;
- c) 10 mM methionine;
- d) 0.1% (w/v) PS20; and
- e) a pH of 5.5.

[0132] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.5% (w/v) of poloxamer 188; and

- e) a pH of about 5.5.

[0133] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.5% (w/v) poloxamer 188; and
- e) a pH of 5.5.

[0134] In certain embodiments, the stable liquid pharmaceutical formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202) ;
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 0.5% (w/v) poloxamer 188; and
- e) a pH of 5.5.

[0135] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody, the anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 240 mM of trehalose;
- d) about 0.5% (w/v) of poloxamer 188;
- e) about 10 mM of methionine; and
- f) a pH of about 5.5.

[0136] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;

- e) 0.5% (w/v) poloxamer 188; and
- f) a pH of 5.5.

[0137] In certain embodiments, the stable liquid pharmaceutical formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202) ;
- b) 10 mM His/HCl;
- c) 240 mM trehalose;
- d) 10 mM methionine;
- e) 0.5% (w/v) poloxamer 188; and
- f) a pH of 5.5.

[0138] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 260 mM of sucrose;
- d) about 0.1% (w/v) of PS20; and
- e) a pH of about 6.0.

[0139] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 0.1% (w/v) PS20; and
- d) a pH of 6.0.

[0140] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 0.1% (w/v) PS20; and
- d) a pH of 6.0.

[0141] In certain embodiments, provided herein is stable liquid pharmaceutical composition or formulation comprising:

- a) about 150 mg/mL of an anti-CD38 antibody or an antigen-binding fragment or equivalent thereof comprising: a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1, a HCDR2 amino acid sequence of SEQ ID NO: 2, and a HCDR3 amino acid sequence of SEQ ID NO: 3, and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 4, a LCDR2 amino acid sequence of SEQ ID NO: 5, and a LCDR3 amino acid sequences of SEQ ID NO: 6; or a VH of SEQ ID NO: 7 and a VL of SEQ ID NO: 8;
- b) about 10 mM of histidine/HCl and/or pharmaceutically acceptable histidine salt;
- c) about 260 mM of sucrose;
- d) about 0.1% (w/v) of PS20;
- e) about 10 mM of methionine; and
- f) a pH of about 6.0.

[0142] In certain embodiments, the stable liquid pharmaceutical composition or formulation comprises:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 10 mM methionine;
- d) 0.1% (w/v) PS20; and
- e) a pH of 6.0.

[0143] In certain embodiments, the stable liquid pharmaceutical composition or formulation consists of:

- a) 150 mg/mL of felzartamab (HIB202/MOR202);
- b) 10 mM His/HCl, 260 mM sucrose;
- c) 10 mM methionine;
- d) 0.1% (w/v) PS20; and
- e) a pH of 6.0.

Methods of Treatment

[0144] Disclosed herein, in certain embodiments, are methods of treating a disease or condition which is amenable to treatment with an anti-CD38 antibody (*e.g.*, felzartamab) or an antigen-binding fragment or equivalent thereof in a subject (*e.g.* a human), comprising administering a pharmaceutical formulation disclosed herein to a subject in an amount effective to treat the disease or condition. In certain embodiments, the disease or condition is an inflammatory disease

or disorder. In certain embodiments, the disease or condition is an autoimmune disease or disorder. In certain embodiments, the disease or condition is an autoantibody-driven disease or disorder. In certain embodiments, the autoantibody-driven disease or disorder is anti-PLA2R autoantibody-mediated membranous nephropathy. In certain embodiments, the autoantibody-driven disease or disorder is anti-THSD7A autoantibody-mediated membranous nephropathy. In certain embodiments, the autoantibody-driven disease or disorder is idiopathic membranous glomerulonephritis. In certain embodiments, the autoantibody-driven disease or disorder is IgA nephropathy. In certain embodiments, the autoimmune disease or disorder is rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, type I diabetes, Addison's disease, autoimmune gastritis, autoimmune hemolytic anemia, autoimmune myopathy, autoimmune orchitis, autoimmune pancreatitis, autoimmune thyroiditis, Grave's disease, myasthenia gravis, pemphigus vulgaris, pernicious anemia, primary biliary cholangitis, primary biliary cirrhosis, anti-NMDA-encephalitis, inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome, multiple sclerosis (MS), systemic sclerosis, autoimmune myocarditis, Kawasaki disease, coronary artery disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease, autoimmune thyroiditis, scleroderma, systemic sclerosis, osteoarthritis, atopic dermatitis, vitiligo, graft vs. host disease, Sjogren's syndrome, autoimmune nephritis, Goodpasture's syndrome, chronic inflammatory demyelinating polyneuropathy, ANCA-associated vasculitis, uveitis, scleroderma, autoimmune bullous skin disease (*e.g.*, bullous pemphigoid), dermatomyositis-polymyositis, epidermolysis bullosa, keratoconjunctivitis sicca, pemphigus foliaceus, Goodpasture's disease, Guillain-Barre syndrome, Hashimoto's disease, idiopathic interstitial pneumonias, idiopathic thrombocytopenia (ITP), neuromyelitis optica, ovarian insufficiency, Celiac disease, chronic immune polyneuropathy, Alzheimer's Disease, amyotrophic lateral sclerosis, Huntington's Chorea, cystic fibrosis, gout, age-related macular degeneration, allergy, asthma, antiphospholipid syndrome (APS), atherosclerosis, C3 glomerulopathy, ischemia/reperfusion injury, peritonitis, sepsis, or any other autoimmune disease resulting from acute or chronic inflammation. In certain embodiments, the autoimmune disease or disorder is an immune complex-mediated disease, including but not limited to immune complex-mediated kidney disease, such as IgA nephropathy, lupus nephritis, Henoch Schönlein purpura nephritis (IgA vasculitis), post-streptococcal glomerulonephritis, and drug-induced immune complex-mediated diffuse proliferative glomerulonephritis. In certain embodiments, the IgA nephropathy is a galactose-deficient IgA1 antibody (Gd-IgA1)-positive and anti-galactose-deficient IgA1 antibody (anti-GD-IgA1)-positive IgA nephropathy. In certain embodiments, the autoimmune disease or

disorder is antibody-mediated transplant rejection (AMR). In certain embodiments, the AMR relates to transplant of an organ selected from the group consisting of kidney, heart, liver, lung, pancreas, stomach, skin, or intestine.

[0145] In certain embodiments, the pharmaceutical formulation disclosed herein is formulated for subcutaneous administration to a subject. In certain embodiments, the pharmaceutical formulation disclosed herein is formulated for intramuscular administration to a subject.

[0146] In certain embodiments, the present disclosure provides for a pharmaceutical formulation according to the present disclosure for therapeutic use, such as the treatment of any one of the aforementioned inflammatory (*e.g.*, autoimmune) diseases or disorders.

[0147] In certain embodiments, the present disclosure provides an injection device comprising a stable anti-CD38 antibody formulation described herein. In the context of subcutaneous administration, a formulation disclosed herein may be administered via a suitable device, such as a syringe, an automatic injection device, an infusion pump, an injector pen, or a needleless injection device.

[0148] The pharmaceutical formulation of the pharmaceutically active anti-CD38 antibody in accordance with the disclosure can be administered as subcutaneous injection, whereby the administration is repeated multiple times at intervals of 1, 2, 3, or 4 weeks. In certain embodiments, the pharmaceutical formulation of the pharmaceutically active anti-CD38 antibody is administered once every week or once every two weeks. The full volume of the injection fluid is in most cases administered within a period of 1 to 60 minutes, *e.g.*, 1 to 10 minutes, 2 to 6 minutes, or 1 to 3 minutes.

Packages, Kits, and Pre-Filled Containers

Also provided herein are kits containing a pharmaceutical composition disclosed herein in suitable container means.

In certain embodiments, disclosed herein is a container means comprising a pharmaceutical formulation described herein. In certain embodiments, the container means is any suitable container including, but not limited to, a vial, syringe, bottle, and an intravenous (IV) bag or ampoule. A syringe holds any volume of liquid suitable for injection of a pharmaceutical formulation disclosed herein into a subject, including, but not limited to, 0.5 cc, 1 cc, 2 cc, 5 cc, 10 cc, or more.

Provided herein are kits comprising a pharmaceutical formulation described herein. In certain embodiments, provided herein is a kit for treating a subject having an inflammatory disease or

disorder (*e.g.*, an autoimmune disease or disorder) comprising a pharmaceutical formulation as described herein and, optionally, an additional therapeutic agent.

In certain embodiments, provided herein is a kit as described above and a label attached to or packaged with the container, the label describing use of a pharmaceutical formulation of the disclosure, optionally, in combination with an additional therapeutic agent.

In certain embodiments, the container means of the kits will generally include at least one vial, test tube, flask, bottle, ampoule, syringe, an intravenous (IV) bag, and/or other container means, into which a pharmaceutical formulation of the disclosure is placed, and/or preferably, suitably aliquoted. Provided herein is a container means comprising a pharmaceutical formulation described herein.

In certain embodiments, kits also include printed material for use of the materials in the kit. In certain embodiments, packages and kits further include a label specifying information required by U.S. FDA or similar regulatory authority, *e.g.*, a product description, amount and mode of administration, and/or indication of treatment. In certain embodiments, packages provided herein include any of the compositions as described herein.

The term “packaging material” refers to a physical structure housing the components of the kit.

In certain embodiments, the packaging material maintains the components sterile and is made of material commonly used for such purposes (*e.g.*, paper, corrugated fiber, glass, plastic, foil, ampules, *etc.*). In certain embodiments, the label or packaging insert includes appropriate written instructions (*e.g.*, instructing the user of the kit to perform one or more methods disclosed herein). Kits, in certain embodiments, additionally include labels or instructions for using the kit components in any method of the disclosure. In certain embodiments, a kit includes a compound in a pack or dispenser together with instructions for administering the compound in a method described herein.

In certain embodiments, instructions include instructions for practicing any of the methods described herein including treatment methods. In certain embodiments, instructions additionally include indications of a satisfactory clinical endpoint or any adverse symptoms that occur, or additional information required by regulatory agencies such as the FDA for use on a human subject.

EXAMPLES

[0149] The following examples are put forth to provide those of ordinary skill in the art with a description of how the compositions and methods described herein may be used, made, and

evaluated, and are intended to be purely exemplary of the disclosure and are not intended to limit the scope of what the inventors regard as their invention.

Introduction

[0150] Felzartamab (HIB202/MOR202) is a fully human monoclonal antibody that specifically binds to human CD38 and is currently being investigated in clinical trials for treatment of different indications.

[0151] Described below is the development of a highly concentrated liquid formulation (HCLF) for felzartamab intended for subcutaneous injection. The five Examples below describe the underlying formulation development activities (see also **FIG. 1**). Different excipients and pH ranges were screened at a protein concentration of 10 mg/mL (**Example 1**). In an HCLF feasibility study, felzartamab solution was concentrated to 150 mg/mL followed by physico-chemical stability assessment after two weeks of incubation at 50°C (**Example 2**). Potential final excipient candidates were screened for their effect on protein-protein interactions by determining the interaction parameter k_D (**Example 3**). To prevent potential subvisible particle formation, several detergents were screened (**Example 3**) before the previously found parameters were combined in a final DOE setup (HCLF optimization) to obtain the excipient concentrations (**Example 4**).

[0152] Based on the outcome of the final DOE (**Example 5**), six formulations were selected and used for the investigation of felzartamab in a long-term stability study for up to 24 months. The below Examples contain data representing up to 12 months of formulation storage time.

Methods

UV spectroscopy

[0153] Protein concentration was determined by UV spectroscopy.

UHP- Size Exclusion Chromatography

[0154] Ultra-high performance size-exclusion chromatography (UHP-SEC) separates molecules according to differences in their hydrodynamic radius. Samples were diluted in respective formulation buffer to 1 mg/mL (for screening experiments) or 2 mg/mL (for high concentration liquid formulation (HCLF) stability assessment). The injection volume was set to 0.75 μ L, which equals a column load to 0.75 μ g (screening) or to 2 μ g (HCLF stability). In each sequence, a reference standard (RF41908) was included before and after sample measurements. Formulation buffers were included as controls to identify formulation matrix-related UV signals.

Chromatography was performed using a 200 Å, 4.6 × 150 mm SEC column and a mobile phase containing 50 mM sodium phosphate and 400 mM sodium perchlorate, pH 6.0. Eluting species were detected by UV absorption at 210 nm and 280 nm.

Particle Detection

[0155] For determination and quantification of subvisible particles, a particle analysis instrument equipped with a 20× objective and flow cell (FOV 50) (50 µm × 350 µm) was used. For adjustment of the focus, the default autofocus function was performed by using 15 µm polystyrene beads for calibration. Count Cal Standard was used to verify correct quantification. Particle images were obtained by using 300 µL sample with a flow rate of 0.03 mL/min and an auto-image frame rate of 29 frames per second. For particle identification the following parameters were used: 3 µm distance to nearest neighbor and particle segmentation thresholds of 10 and 13 for light and dark particle, respectively. Particle size reported represents the equivalent spherical diameter (ESD).

Light Obscuration

[0156] Subvisible particle level was assessed by light obscuration using particle counting systems. Samples were measured undiluted directly from the vial. The instrument was placed under a laminar flow to reduce artificial intake of particles from lab environment. Samples were degassed before measurement. A volume of 0.5 mL was used for each run. Two runs were executed per sample. The results are reported as particles per mL. Particle numbers were reported as cumulative particles ≥2 µm, ≥5 µm, ≥10 µm, ≥15 µm, and ≥25 µm.

[0157] In addition to an initial water measurement, water and formulation buffer were measured. The device was flushed with approximately 10 mL water after each sample.

Capillary Gel Electrophoresis (CGE)

[0158] The purpose of CGE is to quantify protein fragments under reduced or non-reduced denaturing conditions. The protein sample is prepared in presence of sodium dodecyl sulphate (SDS), an anionic surfactant which is adsorbed at the protein surface. The charge per protein molecule correlates roughly with the molecular weight. Within the capillary matrix, separation based on charge takes place by an electrical field. Samples were diluted from 10 mg/mL to 2 mg/mL in SDS-MW sample buffer at pH 7.3 and incubated in iodoacetic-acid for 10 min at 70°C. Subsequently, samples were centrifuged for 1 min at 10,000 rpm to remove air bubbles.

Capillary Zone Electrophoresis (CZE)

[0159] CZE was performed to analyze heterogeneity of charged antibody variants. Charged variants and related isoforms were separated according to their isoelectric point. Prior to measurements, samples were diluted to a concentration of 1 mg/mL with purified water in sample tubes. Separation was performed at 30.0 kV for 18 min. Before separation, capillaries were rinsed with 0.1% HCl for 5 min and 10 min with 400 mM EACA (6-aminocaproic acid), 2 mM TETA (triethylenetetramine), pH 5.7, and 1% HPMC (hydroxypropylmethyl cellulose) buffer. Separation was performed in 380 mM EACA, pH 5.7 and 0.05% HPMC.

Thermal Stability

[0160] Thermal unfolding experiments were performed using conventional methods. Determination of melting temperature (T_m) is based on intrinsic fluorescence of the protein. Intrinsic fluorescence was excited at 280 nm and emission was monitored at 330 nm and 350 nm. In addition, turbidity of the sample was assessed by back reflection optics. 10 μ L of the sample was loaded into a single capillary. Bovine serum albumin (BSA; 2 mg/mL) was included as a control for melting point determination. Samples were heated from 25°C to 95°C with a heating ramp of 1°C/min.

Viscosity

[0161] Viscosity was measured with disabled stray light correction. Caffeine was used as a reference standard to ensure system suitability with respect to seizing and dynamic viscosity. Samples were measured in triplicates at 20°C. Briefly, the sample runs through a solvent filled capillary. A UV detector recorded the time between distinct detection windows and compared it to a reference with known viscosity.

Visible Particles

[0162] Visible particles were determined by visual inspection according to standardized protocols. Quantity of visible particles was estimated and categorized according to the following: 0 (no particles observed) = category I, 1-10 particles observed = category II, 10-20 particles observed = category III, and >20 particles observed = category IV.

Dynamic Light Scattering (DLS)

[0163] Arginine and histidine acid and base variants were investigated to find the optimal excipient combination for targeted pH level. Diffusion interaction parameter (kD) values were

determined by measuring diffusion coefficients (D) at 25°C using eight protein concentrations between 0.3 mg/mL and 40 mg/mL. Each well was analyzed with five acquisitions and an acquisition time of 5 s at 25°C. The diffusion interaction parameter was calculated as linear fit of mutual diffusion coefficient D versus protein concentration to obtain the diffusion coefficient at infinite dilution D_0 . The slope of the linear fit corresponds to the interaction parameter kD . Prior to DLS measurements, felzartamab drug substance ($V = 1.0$ mL) was dialyzed against 500 mL respective formulation buffer over night at 2-8°C. Post dialysis samples were diluted to 0.3 mg/mL, 0.6 mg/mL, 1.25 mg/mL, 2.5 mg/mL, 5.0 mg/mL, 10 mg/mL, 20 mg/mL with respective formulation buffer and analyzed by DLS.

Self-Interaction using Bio-Layer Interferometry

[0164] Interferometry (or “Bio-Layer Interferometry” or “BLI”) is an optical, label-free detection method to perform real-time measurements of a molecule’s binding to a sensor modified with a specific ligand or other sensitive layer. During the measurement, the sensors were inserted into the samples provided in 96- or 384-well-MTPs, *i.e.*, samples were not consumed by the experiment.

[0165] Using anti-human Fc antibody coated sensors (AHC), it is possible to capture a human antibody of interest. After saturating unoccupied anti-Fc binding sites on the sensor with human Fc protein (hu Fc), the sensor was dipped into a well containing the same antibody in solution. An increasing signal was interpreted as antibody self-interaction.

Example 1: Excipient screening

[0166] Contribution of single excipients and their impact on protein aggregation and self-interaction propensity at a moderate protein concentration (10 mg/mL) was investigated across multiple formulations. Histidine-acetate was chosen as initial buffer for testing at a pH range from 5.0 to 6.0. Felzartamab drug substance was dialyzed overnight at 2-8°C (dialysis cassettes, MWCO 10 kDa) against 50 mM histidine-acetate buffer at pH 5.0 and pH 6.0, respectively. After dialysis, protein concentration was adjusted to 50 mg/mL by dilution with respective buffer. The final protein concentration was targeted to 10 mg/mL.

[0167] To investigate the effects of pH, buffer strength, arginine, NaCl, trehalose, and proline, a Design of Experiments (DOE) methodology with a fractional factorial pseudo resolution V+ design was used at an $\alpha = 0.05$ significance level (confidence interval of 95%). Table 2 shows the tested excipient combinations. Formulations were labelled according to a formulation ID

(N1-N35). N36 served as a stability reference (10 mM His/HCl, 260 mM sucrose, 0.1% (v/v) PS20, pH 6.0).

Table 2: Tested excipient combinations in Screening (Step 1)

Formulation ID	Histidine-acetate [mM]	Arginine [mM]	NaCl [mM]	Trehalose [mM]	Proline [mM]	pH
N1	10	0	0	0	250	5.0
N2	10	0	0	0	0	6.0
N3	50	0	0	0	0	5.0
N4	50	0	0	0	250	6.0
N5	10	100	0	0	0	5.0
N6	10	100	0	0	250	6.0
N7	50	100	0	0	250	5.0
N8	50	100	0	0	0	6.0
N9	10	0	100	0	250	5.0
N10	10	0	100	0	0	6.0
N11	50	0	100	0	0	5.0
N12	50	0	100	0	250	6.0
N13	10	100	100	0	0	5.0
N14	10	100	100	0	250	6.0
N15	50	100	100	0	250	5.0
N16	50	100	100	0	0	6.0
N17	10	0	0	300	0	5.0
N18	10	0	0	300	250	6.0
N19	50	0	0	300	250	5.0
N20	50	0	0	300	0	6.0
N21	10	100	0	300	250	5.0
N22	10	100	0	300	0	6.0
N23	50	100	0	300	0	5.0
N24	50	100	0	300	250	6.0
N25	10	0	100	300	0	5.0

Formulation ID	Histidine-acetate [mM]	Arginine [mM]	NaCl [mM]	Trehalose [mM]	Proline [mM]	pH
N26	10	0	100	300	250	6.0
N27	50	0	100	300	250	5.0
N28	50	0	100	300	0	6.0
N29	10	100	100	300	250	5.0
N30	10	100	100	300	0	6.0
N31	50	100	100	300	0	5.0
N32	50	100	100	300	250	6.0
N33	30	50	50	150	125	5.5
N34	30	50	50	150	125	5.5
N35	30	50	50	150	125	5.5
N36	10 mM Histidine/HCl, 260 mM sucrose, 0.1% (v/v) PS20, pH 6.0					

Results and Summary:

Monomer Content and Aggregates in Screening Formulations

[0168] Monomer content and aggregates denoted as high-molecular weight species (HMW) and fragments (low molecular weight species, LMW) were assessed for formulations N1 to N35 after one and two weeks of storage at 50°C under uncontrolled humidity conditions by UHP-SEC. UHP-SEC results are shown in Table 3. Aggregation tendency findings are shown **FIG. 2** as results of a multi-linear regression (MLR) analysis. The MLR model relates the monomer content of a formulation by a linear regression to a set of independent variables, including trehalose, arginine, proline, combination of arginine and NaCl, pH, NaCl, and buffer strength.

Table 3: Monomer and aggregate contents determined by UHP-SEC of screening formulations after one and two weeks of storage at 50°C.

ID	Monomer [%]			HMW [%]			LMW [%]		
	T0	T1w 50°C	T2w 50°C	T0	T1w 50°C	T2w 50°C	T0	T1w 50°C	T2w 50°C
N1	94.5	91.6	84.8	4.8	5.8	10.4	0.6	2.6	4.8
N2	94.0	92.2	86.3	5.5	5.8	9.9	0.4	2.0	3.8
N3	95.7	84.9	76.5	3.9	12.4	18.8	0.4	2.7	4.8
N4	95.9	86.6	75.7	3.4	10.5	18.7	0.6	2.9	5.6
N5	96.3	81.8	66.6	3.2	15.6	28.9	0.5	2.6	4.5

ID	Monomer [%]			HMW [%]			LMW [%]		
	T0	T1w 50°C	T2w 50°C	T0	T1w 50°C	T2w 50°C	T0	T1w 50°C	T2w 50°C
N6	96.6	80.8	62.1	2.9	16.3	33.1	0.5	2.9	4.8
N7	96.6	77.5	58.0	2.8	19.5	37.0	0.6	3.0	4.9
N8	96.6	83.4	73.4	2.8	14.0	22.0	0.6	2.6	4.6
N9	94.5	78.7	70.9	4.8	18.5	24.3	0.7	2.7	4.8
N10	93.6	89.0	84.2	5.8	8.5	11.1	0.6	2.5	4.7
N11	95.7	77.4	80.6	3.8	19.4	13.3	0.5	3.2	6.1
N12	96.1	85.8	72.1	3.5	11.3	22.1	0.5	2.8	5.7
N13	96.1	83.9	71.0	3.4	13.7	24.7	0.5	2.4	4.3
N14	96.4	85.0	70.9	3.0	12.3	24.3	0.5	2.7	4.8
N15	96.6	79.2	67.2	2.9	18.0	28.1	0.6	2.8	4.7
N16	96.5	85.6	75.4	3.0	11.9	20.2	0.5	2.6	4.4
N17	93.5	93.0	89.4	5.9	4.5	6.1	0.6	2.5	4.5
N18	94.7	92.0	87.6	4.8	5.2	7.1	0.5	2.9	5.4
N19	96.0	89.7	84.3	3.4	7.1	10.1	0.6	3.2	5.5
N20	95.9	90.9	86.2	3.6	6.3	9.0	0.6	2.8	4.8
N21	96.7	86.4	76.6	2.8	10.4	18.3	0.5	3.2	5.1
N22	96.2	87.7	80.9	3.2	9.0	13.5	0.6	3.3	5.6
N23	96.4	87.8	83.5	3.0	9.1	11.3	0.6	3.1	5.2
N24	96.6	86.6	80.3	2.8	10.1	14.1	0.6	3.3	5.5
N25	93.7	86.3	81.9	5.7	10.7	13.0	0.6	3.0	5.1
N26	94.6	89.1	83.5	4.8	8.0	11.2	0.7	2.9	5.3
N27	96.2	84.4	80.0	3.4	12.4	14.4	0.5	3.2	5.6
N28	95.9	88.7	84.0	3.6	8.0	10.2	0.5	3.4	5.8
N29	96.5	86.6	77.9	2.9	10.4	17.0	0.6	3.0	5.1
N30	96.4	88.1	80.6	3.1	8.8	14.1	0.5	3.2	5.2
N31	96.5	87.8	82.7	2.9	9.3	12.3	0.6	2.9	5.0
N32	96.6	89.0	82.4	2.8	8.2	13.0	0.6	2.8	4.6
N33	96.2	88.8	83.9	3.3	8.6	11.7	0.5	2.6	4.4
N34	96.2	89.1	84.5	3.3	8.3	11.2	0.5	2.6	4.3
N35	96.0	88.9	83.5	3.4	8.5	12.1	0.6	2.6	4.4

[0169] All tested samples showed an increase in HMW species associated with a decrease in monomer content. The formation of HMW species was more pronounced in comparison to LMW species which indicated an aggregation propensity of the tested protein. The top candidates with best colloidal stability (less decrease in monomer content) after two weeks of storage at 50°C were formulation variants N17 and N18, both containing a high amount (300 mM) of trehalose.

Protein Fragmentation of Screening Formulations

[0170] CGE under non-reducing conditions was used to track potential formation of fragments after incubation of one and two weeks at 50°C. The electropherogram of felzartamab exhibited one IgG main peak, peak b, seven LMW peaks, and one HMW1 peak. Peak b corresponds to a heavy-heavy-light (HHL) species in which one light chain of the IgG is lost. The LMW peaks largely correspond to IgG fragments. The HMW1 peak corresponds to IgG aggregates. Table 4 and Table 5 show relative peak areas of samples N1 to N35 stressed at 50°C for one and two weeks, respectively, and subsequently analyzed by CGE under non-reduced conditions. The reference solution included 10 mg/mL felzartamab, 10 mM Histidine, 260 mM sucrose, 0.1% PS20, pH 6.0.

Table 4: Relative peak areas determined by CGE under non-reduced conditions after one week of storage.

ID	Main purity [%]	Peak b	LMW 1	LMW2	LMW 3	LMW 4	LMW 5	LMW 6	LMW 7	HMW 1
Ref. (n=20)	91.1 ± 2.0	3.3 ± 0.3	1.1 ± 0.3	0.4 ± 0.2	0.7 ± 0.1	0.3 ± 0.1	1.1 ± 0.3	1.1 ± 0.3	0.3 ± 0.1	0.9 ± 0.5
N1	91.7	2.2	0.9	0.7	0.9	0.9	0.6	1.7	0.3	0.3
N2	91.9	2.5	1.0	0.5	1.0	0.8	0.5	1.4	0.2	0.2
N3	93.0	0.9	0.5	1.0	0.9	1.1	0.5	1.6	0.3	0.3
N4	91.6	2.0	1.0	0.7	1.0	0.8	0.5	1.8	0.2	0.4
N5	93.3	0.9	0.5	0.9	0.7	1.0	0.5	1.6	0.3	0.6
N6	92.4	1.2	0.7	1.1	0.8	0.9	0.6	1.8	0.3	0.3
N7	93.0	0.9	0.6	1.0	0.6	1.0	0.4	1.9	0.5	0.2
N8	93.0	1.2	0.6	0.9	0.9	1.0	0.4	1.5	0.3	0.2
N9	92.2	1.3	0.6	1.1	0.8	0.9	0.5	2.1	0.3	0.3
N10	92.2	1.9	0.9	0.9	0.8	0.6	0.6	1.9	0.2	0.2
N11	92.3	0.8	0.6	1.3	0.8	1.1	0.3	2.2	0.3	0.3
N12	91.8	1.8	0.9	0.8	0.9	0.8	0.5	1.9	0.2	0.3
N13	93.0	1.2	0.5	1.0	0.8	0.8	0.5	1.6	0.3	0.2
N14	92.9	1.4	0.6	0.9	1.0	0.8	0.5	1.6	0.2	0.2
N15	93.2	0.8	0.5	1.1	1.0	0.8	0.4	1.8	0.3	0.2
N16	93.4	1.3	0.6	0.7	0.8	0.7	0.4	1.5	0.2	0.3
N17	91.6	2.2	0.8	0.7	1.0	0.7	0.5	1.5	0.3	0.6
N18	90.2	2.7	1.0	0.6	0.9	0.8	0.7	2.0	0.4	0.7
N19	91.3	1.7	0.7	0.9	0.9	0.8	0.6	2.0	0.6	0.5
N20	90.9	2.2	0.9	0.6	0.8	0.8	0.7	2.0	0.5	0.7
N21	89.8	2.1	0.9	0.7	0.9	0.8	0.7	2.2	0.5	1.45
N22	89.8	2.4	0.9	0.6	0.8	0.8	0.7	2.3	0.6	1.07
N23	91.2	1.5	0.6	1.1	0.8	0.7	0.7	2.1	0.7	0.62
N24	89.6	2.2	0.9	0.7	0.9	0.9	0.9	2.3	0.6	1.27

ID	Main purity [%]	Peak b	LMW 1	LMW2	LMW 3	LMW 4	LMW 5	LMW 6	LMW 7	HMW 1
N25	89.4	1.9	0.6	1.0	1.0	1.0	0.9	2.4	0.7	1.05
N26	89.8	2.5	1.0	0.8	0.9	0.8	0.7	2.2	0.5	0.9
N27	91.0	1.5	0.6	1.2	0.9	0.6	0.7	2.3	0.6	0.67
N28	89.8	2.2	1.1	0.8	n.a.	0.8	0.7	2.5	0.5	0.74
N29	90.1	1.6	0.7	1.1	0.9	0.8	0.8	2.1	0.7	1.25
N30	89.1	2.4	0.9	0.9	n.a.	0.9	0.8	2.5	0.5	0.87
N31	90.9	1.6	0.7	1.1	n.a.	0.5	0.6	2.1	0.7	0.95
N32	91.1	1.9	0.7	0.8	0.8	0.6	0.7	1.9	0.6	0.93
N33-N35 (CP)	92.9	2.9	0.9	0.3	0.9	0.5	0.6	0.6	0.3	0.2

Table 5: Relative peak areas [%] determined by CGE under non-reduced conditions after two weeks of storage.

ID	IgG purity [%]	Peak b	LMW1	LMW2	LMW3	LMW4	LMW5	LMW6	LMW7	HMW1
Ref. (n=20)	91.1 ± 2.0	3.3 ± 0.3	1.1 ± 0.3	0.4 ± 0.2	0.7 ± 0.1	0.3 ± 0.1	1.1 ± 0.3	1.1 ± 0.3	0.3 ± 0.1	0.9 ± 0.5
N1	87.8	2.1	1.1	1.3	0.9	1.2	0.6	3.0	0.8	1.3
N2	89.6	2.2	1.1	1.0	0.8	1.1	0.4	2.5	0.6	0.7
N3	88.8	1.1	0.9	1.8	0.8	1.2	0.4	3.4	1.0	0.7
N4	86.6	2.2	1.8	1.4	1.0	1.1	0.5	4.0	0.8	0.7
N5	88.7	1.0	0.9	0.1	2.8	1.4	0.3	3.5	0.8	0.4
N6	86.2	1.3	0.8	2.7	1.0	1.2	0.4	4.2	1.1	1.2
N7	87.8	1.1	0.8	2.4	0.9	1.0	0.3	4.0	1.1	0.7
N8	89.6	1.1	0.8	1.6	0.8	1.1	0.5	3.4	0.7	0.5
N9	87.7	1.6	0.7	1.9	0.9	1.1	0.4	3.7	0.9	1.0
N10	89.0	2.1	1.0	1.3	0.8	0.8	0.5	3.3	0.6	0.8
N11	87.0	1.2	0.9	2.2	0.9	1.2	0.2	4.2	1.0	1.1
N12	86.4	2.2	1.2	1.7	0.9	1.0	0.4	4.3	0.9	1.1
N13	90.0	1.3	1.0	1.9	0.7	1.0	0.3	3.0	0.5	0.2
N14	88.3	1.7	1.3	1.6	1.0	0.8	0.5	3.6	0.9	0.3
N15	88.0	1.3	1.2	2.0	0.8	1.0	0.4	3.8	1.1	0.4
N16	89.3	1.6	0.8	1.6	1.0	1.0	0.5	3.1	0.7	0.5
N17	88.6	2.4	1.3	1.3	1.0	0.9	0.6	2.9	0.8	0.3
N18	87.4	3.0	1.9	0.9	1.0	1.0	0.5	3.3	0.5	0.4
N19	87.5	1.6	1.0	1.6	0.9	1.0	0.6	3.6	1.1	1.1
N20	88.0	2.5	1.3	1.1	1.0	1.0	0.5	3.2	0.8	0.7

ID	IgG purity [%]	Peak b	LMW1	LMW2	LMW3	LMW4	LMW5	LMW6	LMW7	HMW1
N21	86.8	2.2	1.5	1.5	1.0	0.8	0.5	3.6	1.0	1.1
N22	87.3	2.4	1.5	1.4	0.9	0.9	0.5	3.6	0.7	0.9
N23	89.1	1.4	1.2	1.7	0.9	0.8	0.5	3.1	0.8	0.4
N24	87.6	2.4	1.4	1.3	1.0	0.8	0.5	3.6	0.7	0.9
N25	88.6	1.8	0.8	1.8	1.0	0.8	0.6	3.4	0.8	0.6
N26	86.7	3.0	1.5	1.2	1.0	0.8	0.6	3.6	0.7	1.1
N27	88.2	1.4	0.9	1.8	1.0	0.8	0.6	3.7	1.0	0.5
N28	86.7	2.5	1.5	1.4	0.9	1.1	0.5	3.8	0.8	0.9
N29	87.6	1.6	1.1	1.7	1.3	0.8	0.6	3.6	1.1	0.7
N30	87.6	2.4	1.3	1.5	0.9	0.9	0.5	3.5	0.8	0.6
N31	88.2	1.6	1.5	2.0	1.0	0.8	0.5	3.0	0.8	0.6
N32	89.2	2.0	0.8	1.6	0.9	0.6	0.5	3.1	0.8	0.7
N33	89.0	2.3	0.8	1.3	0.9	0.7	0.6	2.9	0.8	0.7
N34	88.8	2.3	0.8	1.4	1.0	0.7	0.6	3.0	0.8	0.6
N35	87.0	4.3	1.3	1.1	1.0	0.8	0.6	2.7	0.7	0.4

Self-Interaction Bio-Layer Assay

[0171] The results of the self-interaction Bio-layer assay are shown in Table 6.

Table 6: Self interaction Bio-layer

Sample ID	Capture level [nm]	Response at saturation [nm]	Relative response (Rrel)
N1	0.9	-0.2	-0.2
N2	1.0	0.4	0.4
N3	0.9	0.1	0.1
N4	1.0	0.4	0.5
N5	1.0	0.2	0.2
N6	0.9	0.1	0.1
N7	0.9	0.2	0.2
N8	0.9	0.4	0.4
N9	1.0	0.4	0.4
N10	0.9	0.7	0.7
N11	1.0	0.5	0.5
N12	0.9	0.5	0.6
N13	0.9	0.4	0.4
N14	0.9	0.3	0.3
N15	0.9	0.3	0.3
N16	0.9	0.4	0.4
N17	0.9	-0.1	-0.1

Sample ID	Capture level [nm]	Response at saturation [nm]	Relative response (Rrel)
N18	1.0	0.2	0.2
N19	0.9	0.0	0.0
N20	0.9	0.4	0.4
N21	0.9	0.1	0.1
N22	0.9	0.2	0.2
N23	0.9	0.2	0.2
N24	0.9	0.2	0.2
N25	0.9	0.4	0.4
N26	0.9	0.4	0.4
N27	0.9	0.3	0.3
N28	0.9	0.4	0.4
N29	0.9	0.3	0.3
N30	0.9	0.3	0.4
N31	0.9	0.3	0.4
N32	0.9	0.2	0.2
N33	0.9	0.3	0.3
N34	0.8	0.4	0.4
N35	0.9	0.2	0.3
N36	1.0	0.2	0.2

[0172] The top formulation candidates with the lowest self-interaction propensity were N1, N17, N19. Those formulations were characterized as including:

- N1 (10 mM histidine-acetate, 250 mM proline, pH 5.0)
- N17 (10 mM histidine-acetate, 300 mM trehalose, pH 5.0)
- N19 (50 mM histidine-acetate, 300 mM trehalose, 250 mM proline, pH 5.0).

[0173] The self-interaction analysis revealed a low self-interaction propensity for felzartamab at low pH (pH =5.0) in combination with high molarity of a hydrophilic compound as sugar or an amino acid.

Summary

[0174] The highest impact on prevention of formation of HMW species was seen for an increasing trehalose concentration, which was reflected in a low delta loss of monomer for formulation variant N17 and N18. The beneficial characteristics of trehalose on stability were confirmed in the self-interaction assay. Surprisingly, increasing the arginine or proline concentration negatively impacted colloidal stability and showed detrimental effects on monomer content and tendency of the monoclonal antibody to form visible particles after storage

at 50°C. Moreover, a higher ionic strength (50 mM histidine, 100 mM NaCl, pH 5.0) promoted visible particle formation of felzartamab.

Example 2: High concentration liquid formulation (HCLF) feasibility

[0175] Increased sugar concentrations and potential viscosity-reducing excipients were tested at a target protein concentration of 150 mg/mL. Six selected formulations were concentrated to at least 150 mg/mL to test the feasibility of a HCLF for felzartamab by conducting an extended analytical characterization to assess a broader cQA profile. Initially, felzartamab drug substance (88.5 mg/mL felzartamab, 260 mM sucrose, 10 mM histidine-HCl, pH 6.0) was dialyzed (MWCO 10 kDa) overnight against 3 L of respective formulation buffer at 2-8°C. Table 7 shows tested formulation buffers for HCLF feasibility.

Table 7: Overview of tested formulation buffers for HCLF feasibility assessment

ID	Buffer	Sugar	Excipient	pH
Form 1	10 mM histidine/HCl	260 mM sucrose	-	6.0
Form 2	10 mM histidine/HCl	260 mM sucrose	250 mM proline	6.0
Form 3	10 mM histidine/HCl	260 mM sucrose	-	5.0
Form 4	10 mM histidine/HCl	260 mM trehalose	15 mM sodium chloride	5.0
Form 5	10 mM histidine/HCl	260 mM trehalose	-	6.0
Form 6	10 mM histidine/HCl	90 mM trehalose	90 mM arginine/HCl	6.0

[0176] The dialyzed samples were concentrated with ultracentrifugation tubes (15 mL MWCO 30 kDa) at 3000 relative centrifugal force (rcf) in 40 min steps (15°C). For viscosity profile assessment (viscosity as a function of protein concentration), a portion of the sample was diluted with the respective formulation buffer to obtain lower concentrated protein samples (concentrations below 80 mg/mL).

Stress conditions

[0177] To assess stability, formulation buffers Form 1 to Form 6 were subjected to three different storage temperatures (2-8°C, 40°C / 75% r.h., and 50°C relative humidity uncontrolled) and analyzed after one and two weeks of storage.

Results and Summary (Step 2):

[0178] Felzartamab was concentrated to ≥ 150 mg/mL and samples were subjected to three different storage temperatures (2-8°C, 40°C / 75% r.h. and 50°C with uncontrolled humidity) to assess colloidal stability. Aggregation propensity of the protein formulations was assessed by UHP-SEC. Results are shown in Table 8 and **FIG. 3**. Most of the formulation buffers showed a protein concentration-dependent aggregation tendency, as indicated by an increase in HMW species. Formulation buffers Form 4 and Form 6 showed an unchanged monomer content at protein concentration above 150 mg/mL, whereas the other formulation buffers showed a slight tendency for formation of HMW species with increasing protein concentration.

Table 8: UHP-SEC results of formulation buffers Form 1 to Form 6 as function of protein concentration. Differences to total of 100% peak area may occur due to rounding.

	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6
Concentration	Monomer [%]					
2 mg/mL	96.4	n.a.	96.2	95.8	96.3	96.5
80 mg/mL	96.5	96.2	96.1	96.5	96.1	96.5
> 150 mg/mL	95.9	91.0	95.5	96.5	95.8	96.5
	HMW [%]					
2 mg/mL	3.4	n.a.	3.6	3.9	3.5	3.3
80 mg/mL	3.4	3.5	3.7	3.3	3.8	3.2
> 150 mg/mL	3.7	9.0	4.2	3.2	3.9	3.2
	LMW [%]					
2 mg/mL	0.2	n.a.	0.2	0.2	0.2	0.2
80 mg/mL	0.2	0.3	0.2	0.2	0.2	0.3
> 150 mg/mL	0.1	0.0	0.3	0.3	0.3	0.2

Stability

[0179] After testing the feasibility of concentrating felzartamab in six formulation variants Form 1 to Form 6 above 150 mg/mL, the samples were subjected to three different storage temperatures: 2-8°C, 40°C, and 50°C. Table 9 shows the UHP-SEC results after one and two weeks of storage. All formulations were characterized by a decrease in monomer content. For storage at 2-8°C after two weeks, the decrease in monomer content was similar for all tested candidates and ranged between 0.5% - 0.8%. For samples stored at 50°C, formulation buffer Form 5 (10 mM His, 260 mM Trehalose, pH 6.0) showed the best performance in maintaining monomer content (ΔT_0 -11.5%), followed by formulation buffer Form 1 (-13.5%). The decrease

in monomer content was mostly related to an increase in HMW species. Those results suggest that trehalose outperforms sucrose in maintenance of monomer content under elevated temperatures.

Table 91: Relative peak areas of monomer at protein concentration of 150 mg/mL for HMW and LMW species after one and two weeks of storage at three different temperatures.

	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6
Monomer [%]						
T0	95.9	96.2	96.4	96.3	95.8	96.2
T1w 2-8°C	95.2	95.5	95.8	95.9	95.2	95.5
T2w 2-8°C	95.4	95.7	95.7	95.5	95.0	95.5
T1w 40°C	93.7	94.0	93.9	93.8	93.3	94.1
T2w 40°C	92.7	93.2	92.8	92.6	92.5	93.0
T1w 50°C	86.9	87.5	86.3	86.2	87.2	87.9
T2w 50°C	82.4	82.1	80.9	79.7	84.3	81.4
Δ (T0-T2w 50°C)	-13.5	-14.1	-15.5	-16.6	-11.5	-14.8
HMW [%]						
T0	3.8	3.6	3.3	3.4	3.9	3.5
T1w 2-8°C	3.8	3.5	3.3	3.2	3.9	3.6
T2w 2-8°C	3.8	3.5	3.4	3.6	4.0	3.6
T1w 40°C	5.0	4.6	4.6	4.6	5.4	4.5
T2w 40°C	5.4	4.9	5.1	5.1	5.7	5.1
T1w 50°C	10.5	9.8	10.9	10.7	10.0	9.5
T2w 50°C	13.6	13.3	14.7	15.4	11.9	14.3
LMW [%]						
T0	0.3	0.2	0.3	0.3	0.3	0.3
T1w 2-8°C	0.8	0.8	0.8	0.8	0.8	0.8
T2w 2-8°C	0.7	0.7	0.7	0.8	0.8	0.8
T1w 40°C	1.1	1.2	1.2	1.4	1.2	1.2
T2w 40°C	1.5	1.7	1.7	1.9	1.5	1.6
T1w 50°C	2.1	2.3	2.3	2.5	2.3	2.1
T2w 50°C	3.2	3.7	3.4	3.9	3.0	3.4

Viscosity

[0180] Viscosity was determined for the highly concentrated protein samples (≥ 150 mg/mL). Large differences in dynamic viscosity were seen among the samples (Table 10). Formulation buffer Form 4 (10 mM Histidine/HCl, 260 mM Trehalose, 15 mM NaCl, pH 5.0) showed the lowest viscosity (13.7 mPas•s). Comparison of formulation buffer Form 1 and Form 3 suggests that lower pH values had a viscosity-lowering effect.

Table 10: Dynamic viscosities for formulation buffers Form 1 – Form 6 determined at protein concentrations of 150 to 170 mg/mL.

ID	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6
Protein concentration [mg/mL]	170	153	167	162	153	164
Viscosity [mPas•s]	21.7	17.6	16.9	13.7	42.9	16.2

Charge Variants

[0181] Charge variant analysis is generally used for characterization of heterogeneity of antibody variants having different charges, which may develop as a result of changes to one or more amino acids (*e.g.*, post-translational modification, conformational change, *etc.*). For tracking of chemical changes, potential changes in charge variants for highly concentrated liquid formulations were analyzed by CZE. Results were recorded as relative main peak (MP) area, acidic peak (AP) group and basic peak (BP) group, as shown in Table 11 and Table 12, which showed measured charge variants for Form 1 to Form 6 stored at 2-8°C and 40°C / 75% r.h. over two weeks. After two weeks of storage no major differences among the formulation buffers were seen. However, for samples stored at 40°C / 75% r.h. the observed decrease in main peak was most prominent for formulation buffer Form 2. Among the candidates, the most promising results were seen for formulation buffers Form 3 and Form 4. Those two are characterized by low pH 5.0 and presence of 260 mM sucrose or trehalose plus a low amount of sodium chloride for the trehalose-based formulation.

Table 11: Charge variants for formulation buffers Form 1-Form 6 stored at 2-8°C over two weeks.

Formulation	Relative peak area [%]								
	T0			T1w 2-8°C			T2w 2-8°C		
	Basic	Main	Acidic	Basic	Main	Acidic	Basic	Main	Acidic
Reference (n=3) *	3.8 ±0.8	63.2±3.0	33.0±3.8	3.8±0.8	63.2±3.0	33.0±3.8	3.8 ±0.8	63.2 ± 3.0	33.0 ±3.8
Form 1	5.4	67.2	27.4	4.9	64.7	30.4	4.9	66.2	28.8
Form 2	5.3	64.3	30.4	5.0	63.3	31.8	4.7	65.4	29.9
Form 3	5.6	63.9	30.5	5.2	63.8	30.9	5.2	68.1	26.7
Form 4	5.8	65.1	29.1	5.4	63.4	31.2	5.4	69.9	24.7
Form 5	4.9	63.2	31.9	4.8	62.3	32.9	5.0	69.0	26.0
Form 6	5.0	62.4	32.6	4.9	63.4	31.7	4.7	67.8	27.5

*Mean value from three time points (T0, T1w, T2w) for Reference: 10 mM Histidine, 260 mM sucrose, 0.1% PS20, pH 6.0.

Table 12: Charge variants for formulation buffers Form 1-Form 6 stored at 40°C / 75% r.h. over two weeks.

Formulation	Relative peak area [%]								
	T0			T1w 40°C / 75% r.h.			T2w 40°C / 75% r.h.		
	Basic	Main	Acidic	Basic	Main	Acidic	Basic	Main	Acidic
Reference (n=3)*	3.8 ±0.8	63.2±3.0	33.0±3.8	3.8±0.8	63.2±3.0	33.0±3.8	3.8 ±0.8	63.2 ± 3.0	33.0 ±3.8
Form 1	5.4	67.2	27.4	5.5	57.4	37.1	6.3	57.3	36.4
Form 2	5.3	64.3	30.4	5.6	57.7	36.7	5.7	55.4	38.9
Form 3	5.6	63.9	30.5	6.7	60.2	33.1	7.8	59.3	32.8
Form 4	5.8	65.1	29.1	8.6	62.4	29.0	8.4	59.1	32.5
Form 5	4.9	63.2	31.9	5.3	59.4	35.3	5.9	56.4	37.7
Form 6	5.0	62.4	32.6	7.0	61.0	32.0	6.5	58.1	35.4

*Mean value from three time points (T0, T1w, T2w) for Reference: 10 mM Histidine, 260 mM sucrose, 0.1% PS20, pH 6.0.

Summary

[0182] Formulation buffers Form 1 to Form 6 (protein concentrations ≥ 150 mg/mL) were analyzed with respect to concentration feasibility and colloidal stability. For all tested formulation buffers, protein concentrations above 150 mg/mL were achieved, thereby fulfilling the antibody content criteria for a HCLF. A higher pH towards 6.0 promoted formation of acidic peak species (decrease in main peak (MP)) and contributed to increased viscosity. Thus, viscosity and acidic species formation were negatively impacted by increasing pH. Arginine was capable of preventing the formation of acidic charged species. Trehalose outperformed sucrose with respect to stability of monomer content (relative scale 0.81 vs. 0.69). Overall, a balanced physico-chemical stability profile was achieved for formulation Form 6 (10 mM histidine/HCl, 90 mM trehalose, and 90 mM arginine at pH 6.0). Based on these observations, the arginine formulation was benchmarked against 10 mM histidine/HCl, 260 mM sucrose, pH 6.0 with respect to detergent compatibility and propensity for particle formation.

Example 3: Detergent screening

[0183] Detergent screening was conducted to assess protein stability in detergent containing formulations. Felzartamab drug substance was concentrated by centrifugation tubes (MWCO 10 kDa) to about 150 mg/mL and dialyzed at 2-8°C (MWCO, 10 kDa) in an approximately 260-fold volume exchange against the following buffers:

- 10 mM histidine/HCl, 260 mM sucrose, pH 6.0
- 10 mM histidine/HCl, 90 mM trehalose, 90 mM arginine, pH 6.0

[0184] Final formulation variants were obtained by spiking of 2% (w/v) polysorbate 20, 2% (w/v) polysorbate 80, or 10% (w/v) poloxamer P188 stock solutions to a final detergent concentration (v/v) according to Table 13.

Table 13: Formulation list for detergent screening at 150 mg/mL antibody

ID	Buffer	Sugar	Excipient	Detergent % (v/v)
F2	10 mM histidine/HCl pH 6.0	260 mM sucrose	-	-
F2a				0.10% PS20
F2b				0.05% PS20
F2c				0.25% Poloxamer P188
F2d				0.50% Poloxamer P188
F2e				0.10% PS80
F2f				0.05% PS80
F6	10 mM histidine/HCl pH 6.0	90 mM	90 mM	-
F6a				0.10% PS20
F6b				0.05% PS20
F6c				0.25% Poloxamer P188

F6d		trehalose	arginine/HCl	0.50% Poloxamer P188
F6e				0.10% PS80
F6f				0.05% PS80

Stress conditions:

[0185] The impact of different detergents on formulation quality was tested with following stress methods.

- I) Samples were placed on a horizontal shaker for one week with a shaking frequency of 9 cycles/min at room temperature.
- II) For testing the feasibility of dilution in saline formulation, variants were diluted in 2R vials from 150 mg/mL to ca. 3.6 mg/mL in 0.9% saline and subsequently incubated for 24 h at 25°C / 60% r.h.
- III) Samples were stored at 150 mg/mL at 2-8°C and 40°C / 75% r.h. for up to two weeks.

Protein Fragmentation:

[0186] To analyze antibody fragmentation, CGE was performed on a microfluidic chip under reduced and non-reduced conditions. Samples were prepared by dilution in respective formulation buffer to 1 mg/mL $\pm$ DTT and heated to 75°C for 5 min. Individual samples were separated by electrophoresis. Protein-lithium-dodecyl-sulfate (LDS)-dye complexes were detected by laser-induced fluorescence. Electropherograms were assessed using conventional methods. The relative peak area of felzartamab light chain (LC) and heavy chain (HC) was calculated and summed up by area under the signal peak for LC and HC peak determined under reducing denaturation conditions. Relative peak areas of LMWS and HMWS peaks were calculated accordingly. The relative main peak area was reported directly from electropherogram determined under non-reducing denaturing conditions.

Light Obscuration

[0187] Subvisible particle level was determined by light obscuration based on a standardized protocol using a particle counter. Samples were measured undiluted directly from the vial. The particle counting system is a light obscuration system and determines the overall size distribution of particles between 2 μ m and 200 μ m. Results are given in particles per mL. Particle numbers were reported as cumulative particles $\geq 2 \mu$ m, $\geq 5 \mu$ m, $\geq 10 \mu$ m, $\geq 15 \mu$ m, and $\geq 25 \mu$ m.

Dynamic Light Scattering (DLS)

[0188] The diffusion interaction parameters (kD) were determined by measuring diffusion coefficients (D) at 25°C using eight protein concentrations: 0.3 mg/mL, 0.6 mg/mL, 1.25 mg/mL, 2.5 mg/mL, 5.0 mg/mL, 10 mg/mL, 20 mg/mL, and 40 mg/mL. The diffusion interaction parameter was calculated as a linear fit of mutual diffusion coefficient D versus protein concentration to obtain the diffusion coefficient at infinite dilution D₀. The slope of the linear fit corresponds to the interaction parameter kD. Tested formulations (excipient variants) are listed in Table 14.

Table 14: Formulation variants for kD value screening

ID	Buffer	Sugar	Excipient	pH	Rationale
F6	10 mM Histidine/HCl	90 mM Trehalose	90 mM Arginine/HCl	6.0	pH effect
F7		90 mM Trehalose	90 mM Arginine/HCl	5.0	
F8		90 mM Trehalose	15 mM NaCl	5.0	Effect of NaCl at low pH
F9		90 mM Trehalose	90 mM NaCl	5.0	
F10		90 mM Sucrose	15 mM NaCl	6.0	Exploratory guess
F11		90 mM Trehalose	90 mM NaCl	6.0	NaCl vs Arginine (F11 vs. F6)

[0189] Table 15 and FIGS. 4A-4B show monomer contents determined by UHP-SEC. After one week of shaking at room temperature, a slight decrease in monomer content was observed which was less pronounced for formulation variants of F6. Concentration of drug substance from 90 mg/mL to 150 mg/mL resulted in a slight loss of monomer (approx. -1.5%) in comparison to felzartamab reference. Overall, all detergents performed similar with respect to prevention of aggregation. A moderate difference in monomer content was seen for the lower poloxamer P188 containing F6 formulation.

Table 15: Monomer content determined by UHP-SEC in detergent screening.

ID	Detergent	T0	T-inuse	T-1w shaking	T2w 2-8°C	T2w 40°C
F2	none	95.5	96.0	95.3	95.3	93.1
F2a	0.1% PS20	95.6	96.1	95.4	95.6	93.1
F2c	0.5%PX188	95.8	96.1	95.4	95.7	93.5
F2e	0.1%PS80	95.4	96.1	95.2	95.8	93.1
F6	none	95.7	96.2	95.7	95.7	93.3
F6a	0.1% PS20	95.6	96.2	95.7	95.9	93.5
F6b	0.05% PS20	95.8	96.2	95.7	95.9	93.6
F6c	0.25% PX188	95.8	96.2	95.7	95.9	90.2
F6d	0.5%PX188	96.0	96.1	95.9	96.1	93.8
F6e	0.1% PS80	95.2	95.8	95.3	95.8	93.3
F6f	0.05% PS80	95.6	96.1	95.5	95.8	93.3
Reference	-	97.0				

Capillary Gel Electrophoresis

[0190] Potential fragmentation was assessed by CGE under reduced (addition of DTT) and non-reducing conditions. Table 16 shows relative peak areas of LC and HC under reduced conditions. Under non-reducing conditions, only main peak species in combination with fragments were observed (Table 17).

Table 16: Results by capillary gel electrophoresis under reducing conditions. Relative peak areas [%] of heavy and light chain were summed up.

Formulation	T0	T-inuse	T-shaking	T2w 2-8°C	T2w 40°C
F2	99.5	99.4	99.5	100.0	100.0
F2a	99.6	99.4	99.5	100.0	99.8
F2d	100.0	99.4	86.7	73.2	62.4
F2e	99.5	99.4	99.5	100.0	95.0
F6	99.4	99.5	99.5	99.5	99.4
F6a	99.4	99.4	99.5	99.5	99.5
F6b	99.4	99.4	99.5	99.4	99.5
F6c	99.0	100.0	99.1	90.8	90.3
F6d	98.8	100.0	82.3	83.1	79.9
F6e	99.4	100.0	99.5	99.5	99.4
F6f	99.4	100.0	99.5	99.5	99.5
Reference	not measured		99.5	100.0	100.0

Table 17: Results by capillary gel electrophoresis under non-reduced conditions for main peak species in %. Remaining relative peak area to 100% refer to low molecular weight species.

Formulation	T0	T-inuse	T-shaking	T2w 2-8°C	T2w 40°C
F2	94.0	92.0	92.0	99.0	100.0
F2a	94.0	91.6	92.7	100.0	98.7
F2d	100.0	90.4	45.7	45.2	40.5
F2e	93.9	91.1	96.0	98.6	97.3
F6	95.2	91.1	96.7	98.3	98.1
F6a	93.6	91.3	96.3	96.4	95.7
F6b	93.7	93.8	94.2	97.4	95.8
F6c	97.3	93.1	56.1	74.7	69.3
F6d	98.3	92.5	36.3	59.5	53.9

F6e	94.5	92.2	94.7	97.4	95.8
F6f	93.7	92.9	96.3	97.3	95.9
Reference	Not measured		95.1	95.1 ± 1.6	

Light Obscuration

[0191] Sub-visible particle levels were determined by light obscuration. Table 18, Table 19, and FIGS. 5A-5C show sub-visible particle levels classified within the range of $\geq 2 \mu\text{m}$ to $\geq 25 \mu\text{m}$ before and after stress conditions. Overall, none of the tested formulation variants revealed critical particle levels for size range $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$ after incubation in 0.9% saline or shaking. According to USP 787 requirements, both levels were well below 6000 and 600 particle per container while assuming a potential injection volume of 1.5 mL. After two weeks of storage at 40°C, only formulation F2d (0.5% poloxamer P188) and formulation F2e (0.1% PS80) formulations exhibited $\geq 25 \mu\text{m}$ sub-visible particle levels.

Table 18: Subvisible particle determination by light obscuration before (T0) and after one day of incubation in 0.9% saline (T-Inuse) or one week of shaking stress (T-shaking) in # per mL. Results represent the average calculated out from two sub-runs.

ID	T0			T-Inuse			T-Shaking		
	$\geq 2 \mu\text{m}$	$\geq 10 \mu\text{m}$	$\geq 25 \mu\text{m}$	$\geq 2 \mu\text{m}$	$\geq 10 \mu\text{m}$	$\geq 25 \mu\text{m}$	$\geq 2 \mu\text{m}$	$\geq 10 \mu\text{m}$	$\geq 25 \mu\text{m}$
F2	5,219	192	37	8,187	278	18	5,091	147	14
F2a	2,792	87	3	260	17	0	3,062	132	7
F2d	3,539	194	12	146	2	0	2,653	87	5
F2e	3,285	115	1	70	3	0	3,584	97	10
F6	2,565	90	13	517	14	3	nd	nd	nd
F6a	2,745	59	1	135	1	0	4,823	125	9
F6b	3,003	95	4	381	4	0	4,596	157	11
F6c	3,533	137	6	125	8	2	4,557	168	12
F6d	2,678	130	10	522	5	0	4,635	140	7
F6e	2,776	80	3	2,715	34	0	4,982	152	8
F6f	2,942	113	14	2,112	11	0	nd	nd	nd

Table 19: Subvisible particle determination by Light obscuration before (T0) and two weeks of storage at 40°C / 75% r.h. in # per mL. Results represent the average calculated out from two sub-runs.

ID	T0			T2w 40°C		
	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm
F2	5,219	192	37	6,770	693	525
F2a	2,792	87	3	2,961	175	85
F2d	3,539	194	12	6,147	1,042	773
F2e	3,285	115	1	3,650	822	712
F6	2,565	90	13	nd	nd	nd
F6a	2,745	59	1	5,610	101	8
F6b	3,003	95	4	nd	nd	nd
F6c	3,533	137	6	nd	nd	nd
F6d	2,678	130	10	3,928	87	9
F6e	2,776	80	3	5,820	98	3
F6f	2,942	113	14	nd	nd	nd

Dynamic Light Scattering (DLS)

[0192] For analyzing excipient/excipient and drug interactions, the effect of pH, arginine, and salt concentration was elaborated according to Table 20 by mutual diffusion coefficient determinations. Overall, all kD values were negative, indicating an aggregation tendency of the antibody molecule. However, a low pH (F6 vs. F7) reduced protein-protein interactions, whereas a higher salt concentration increased them. The lowest kD values were found for F11.

Table 20: kD value determination measured by dynamic light scattering.

ID	Buffer	Sugar	Excipient	pH	Rationale	kD [mL/g]	r ²
F6	10 mM Histidine/HCl	90 mM Trehalose	90 mM Arginine/HCl	6.0	pH effect	-33.3	0.99
F7		90 mM Trehalose	90 mM Arginine/HCl	5.0		-19.4	0.92
F8		90 mM Trehalose	15 mM NaCl	5.0	Effect of NaCl at low pH	-12.2	0.98
F9		90 mM Trehalose	90 mM NaCl	5.0		-33.0	0.96

ID	Buffer	Sugar	Excipient	pH	Rationale	kD [mL/g]	r ²
F10		90 mM Sucrose	15 mM NaCl	6.0	Effect of sugar and pH	-37.6	0.99
F11		90 mM Trehalose	90 mM NaCl	6.0	NaCl vs Arginine (F11 vs. F6)	-51.5	0.95

Visible Particles

[0193] Visual inspection was performed for assessment of presence of visible particles. Results which were obtained throughout the detergent screening are summarized in Table 21. Particle estimation was performed according to the following categorization:

Particle Estimate	Category
0 (no particles observed)	I
1-10	II
10-20	III
>20	IV

[0194] After two weeks of storage at 40°C, all formulation variants were scored with a low particle category (I or II), except for F2 in which a high number of particles was seen (category IV).

Table 21: Visual inspection results of detergent screening study. nd = not determined.

Formulation	T0		T-Inuse		T-shaking		T2w 40°C/75% r.h.	
	Cat.	Qty	Cat.	Qty	Cat.	Qty	Cat.	Qty
F2	II	3	III	10-20	IV	>20	IV	>20
F2 + 0.1% PS20	I	0	II	1	II	3	II	1-3
F2 + 0.5% PX188	I	0	II	6	II	4	II	2-3
F2 + 0.1% PS80	I	0	II	6	II	5-10	I/II	0-3
F6	II	1	II	7	II	2	nd	nd
F6 + 0.1% PS20	II	2	II	3	II	2	II	2-5
F6 + 0.05% PS20	I	0	II	4	II	1	nd	nd
F6 + 0.25% PX188	I	0	II	1	II	3	nd	nd
F6 + 0.5% PX188	I	0	I	0	II	2-5	II	3-5

Formulation	T0		T-Inuse		T-shaking		T2w 40°C/75% r.h.	
	Cat.	Qty	Cat.	Qty	Cat.	Qty	Cat.	Qty
F6 + 0.1% PS80	I	0	II	1	I	0	II	3-5
F6 + 0.05% PS80	I	0	II	2-4	nd	nd	nd	nd

Results and Summary

[0195] Overall, all detergents performed similarly with respect to prevention of aggregation measured by UHP-SEC. For formulation F6 containing 0.25% PX188, a higher portion of aggregates and fragments was observed in comparison to 0.5% PX188. These results suggest that a concentration of PX188 above a critical micelle concentration has a beneficial effect on protein stability. Moreover, the tendency for particle formation was assessed by light obscuration. Assuming a potential injection volume of 1.5 mL for a subcutaneous route of drug administration, the high detergent-containing formulations F2d (0.5% PX 188) and F2e (0.1% PS80) exhibited permitted sub-visible particle levels for $\geq 25 \mu\text{m}$ (6000 per container). All other variants were well within the USP 788 Particulate Matter in Injections test limits. All tested detergents were considered suitable for F6 formulation to prevent particle formation. In addition, kD values were assessed to evaluate potential drug-excipient interaction. It was shown that high repulsive forces (positive charged amino acid residues) present at low pH were beneficial for protein stability. This colloidal characteristic is in agreement with lower observed dynamic viscosity. In a next step, formulation candidate F6 (90 mM trehalose, 90 mM arginine, pH 6.0) was optimized at target felzartamab concentration (150 mg/mL) with respect to final excipient concentration. Polysorbate 20 (0.1%) was chosen as the detergent.

Example 4: HCLF optimization

[0196] Felzartamab drug substance was concentrated with centrifugation tubes (30kDa MWCO) to approximately 150 mg/mL at rcf 3000, 15°C and dialyzed (MWCO, 10 kDa) with approximately 1600-fold volume exchange in two buffer exchanging steps. The first 40-fold volume exchange was performed within 6 h against respective formulation buffer and the second 40-fold volume exchange was performed at 2-8°C over two days. For compensation of osmotic dilution effects after dialysis, formulation variants were re-concentrated to a final protein concentration of $150 \text{ mg/mL} \pm 7.5 \text{ mg/mL}$. Subsequently, final formulation variants N1-N18 (Table 22) were obtained by spiking with 2% (w/v) polysorbate 20 to a final detergent concentration of 0.1% (v/v). A formulation containing 10 mM histidine, 90 mM trehalose, and 90 mM Arginine/HCl was included as a control from feasibility experiments indicated as 'NC'.

Table 22. Formulations for HCLF optimization (step 4) at 150 mg/mL.

ID	pH	Arginine (base) [mM]	Trehalose [mM]	Polysorbate 20 (v/v)	Histidine/HCl [mM]
N1	5.7	0	225	0.1 %	10
N2	5.5	0	240	0.1 %	10
N3	5.5	90	135	0.1 %	10
N4	5.5	90	240	0.1 %	10
N5	5.5	45	180	0.1 %	10
N6	5.7	60	240	0.1 %	10
N7	5.8	90	175	0.1 %	10
N8	6.0	0	225	0.1 %	10
N9	6.0	30	240	0.1 %	10
N10	5.9	90	190	0.1 %	10
N11	6.3	0	240	0.1 %	10
N12	6.2	90	135	0.1 %	10
N13	6.2	90	240	0.1 %	10
N14	6.2	30	225	0.1 %	10
N15	6.2	0	240	0.1 %	10
N16	5.9	45	180	0.1 %	10
N17	5.9	45	180	0.1 %	10
N18	5.9	45	180	0.1 %	10
NC	6.0	90	90	-	10

Results and Summary (Step 4):Stress Conditions:

[0197] Thermal stability of the formulation variants (N1-N18, NC) was assessed by subjecting them to two different storage temperatures and analyzed after two and four weeks of storage.

- 40°C / 75% r.h.
- 50°C (r.h. uncontrolled)

[0198] Intense freeze-thaw stress was simulated by three independent freeze-thaw cycles. Hence, samples were transferred to -80°C and thawed (ca. 1 h) within three repetitive cycles.

KD screening

[0199] Table 23 shows hydrodynamic diffusion interaction kD values of tested acidic/base profiles for felzartamab. The amount of titrant needed to compensate for pH shift due to the addition of arginine differed substantially. Formulation variants F1 and F4 were characterized by the lowest amount needed for pH compensation to target pH 6.0. However, the highest kD values

were achieved by acid/base variants F3 and F5. Conclusively, variant F3 was used for HCLF optimization study because of its highest kD value without using acetic acid for titration.

Table 23: DLS determined kD values of formulation variants listed in Table 21.

ID	Buffer	Sugar	Excipient	Titrant	kD [mL/g]	r ²	pH before adjustment	Added titrant to pH 6.0 [mM]
F1	10 mM His/HCl	90 mM trehalose	90 mM Arg/HCl	NaOH	-28.7	0.99	4.5	2.4
F2	10 mM His (base)	90 mM trehalose	90 mM Arg (base)	HCl	-29.3	0.99	10.1	42.8
F3	10 mM His/HCl	90 mM trehalose	90 mM Arg (base)	HCl	-23.6	0.99	9.9	40.6
F4	10 mM His (base)	90 mM trehalose	90 mM Arg/HCl	HCl	-27.8	0.98	7.1	2.5
F5	10 mM His (base)	90 mM trehalose	90 mM Arg (base)	Acetic acid	-21.8	0.99	10.1	47.5

Aggregation Propensity

[0200] Aggregation propensity was assessed by UHP-SEC. Results are summarized in Table 24 and Table 25. Overall, decrease in monomer content was dominated by formation of higher molecular weight species (HMW1 + HMW 2) in all samples. The highest colloidal stability after elevated temperature storage was seen for formulation variant N2 (240 mM trehalose, pH 5.5, 0.1% (v/v) PS20) and N8 (225 mM trehalose, pH 6.0, 0.1% (v/v) PS20) which have a high amount of trehalose (≥ 225 mM). Both outperformed NC formulation variants. No changes in monomer content after three repetitive freeze thaw cycles were seen in any of the formulation variants. It was shown that arginine contributed to formation of aggregates, which is reflected in observed differences between N2, N8, and NC formulations.

Table 24: Relative main peak areas [%] for samples stored at 40°C / 75% r.h. for two and four weeks. 10 mM histidine, 260 mM sucrose, pH 6.0 was included as analytical reference.

ID	T0			T2w 40°C			T4w 40°C		
	Monomer	HMW	LMW	Monomer	HMW	LMW	Monomer	HMW	LMW
N1	96.0	3.3	0.7	92.7	5.3	1.7	90.1	7.2	2.7
N2	96.0	3.4	0.7	93.1	5.1	1.5	90.8	6.9	2.4
N3	96.2	3.2	0.7	92.8	5.3	1.7	89.4	8.0	2.6
N4	96.1	3.2	0.7	92.7	5.3	1.7	89.2	8.2	2.6
N5	96.1	3.2	0.7	92.9	5.2	1.6	89.8	7.7	2.5

ID	T0			T2w 40°C			T4w 40°C		
	Monomer	HMW	LMW	Monomer	HMW	LMW	Monomer	HMW	LMW
N6	96.0	3.3	0.7	92.4	5.7	1.6	89.2	8.4	2.4
N7	96.0	3.4	0.7	93.5	4.7	1.5	91.6	6.2	2.2
N8	95.7	3.6	0.7	92.6	5.6	1.5	90.2	7.6	2.2
N9	95.8	3.5	0.7	91.5	6.5	1.7	87.4	10.1	2.5
N10	96.0	3.3	0.7	92.0	6.0	1.7	88.1	9.4	2.5
N11	95.5	3.8	0.7	92.2	6.0	1.6	89.8	7.9	2.3
N12	95.8	3.5	0.7	91.8	6.2	1.7	88.0	9.5	2.5
N13	95.8	3.5	0.7	91.9	6.0	1.8	87.7	9.7	2.6
N14	95.6	3.7	0.7	85.7	11.9	2.0	75.2	21.7	3.0
N15	95.5	3.8	0.7	92.1	6.1	1.6	89.5	8.1	2.4
N16	95.8	3.5	0.7	92.2	5.9	1.7	89.0	8.7	2.4
N17	95.7	3.5	0.7	86.2	11.4	2.0	75.7	21.5	2.9
N18	95.7	3.5	0.8	92.1	6.0	1.7	88.7	8.9	2.4
NC	95.7	3.5	0.7	91.2	6.7	1.9	85.4	11.9	2.7
Reference	97.0	2.3	0.7	97.0	2.3	0.7	96.7	2.4	0.9

Table 25: Relative main peak areas for HCLF samples stored at 50°C for two and four weeks and three times repetitive freeze thaw cycles (3x FT) determined by UHP-SEC.

ID	T2w 50°C			T4w 50°C			3x FT		
	Monomer	HMW	LMW	Monomer	HMW	LMW	Monomer	HMW	LMW
N1	77.6	18.5	3.9	63.7	30.7	5.6	95.9	3.4	0.7
N2	80.0	16.6	3.4	67.6	27.6	4.9	95.9	3.5	0.7
N3	68.5	28.0	3.6	52.0	43.0	5.0	96.1	3.3	0.7
N4	70.7	25.6	3.7	54.3	40.7	5.0	96.1	3.2	0.7
N5	72.8	23.8	3.4	56.8	38.5	4.7	96.0	3.3	0.7
N6	73.1	23.4	3.5	57.4	37.8	4.8	95.9	3.4	0.7
N7	72.3	24.6	3.1	59.7	35.7	4.6	95.9	3.4	0.7
N8	79.4	17.4	3.2	67.0	28.5	4.5	95.6	3.7	0.7
N9	74.7	21.6	3.6	60.1	34.8	5.0	95.7	3.6	0.7
N10	71.7	24.6	3.7	55.3	39.8	5.0	95.9	3.5	0.7
N11	78.9	17.7	3.3	66.6	28.5	4.9	95.4	3.9	0.7
N12	70.5	25.8	3.7	53.2	41.9	5.0	95.7	3.6	0.7
N13	73.3	22.9	3.8	57.4	37.4	5.3	95.8	3.5	0.7
N14	72.5	23.1	4.4	57.1	36.9	5.9	95.5	3.8	0.7
N15	78.7	17.8	3.5	66.3	28.8	5.0	95.4	3.9	0.7
N16	73.7	22.8	3.5	58.4	36.9	4.7	95.8	3.6	0.7
N17	71.3	24.7	4.0	55.9	38.7	5.4	95.7	3.6	0.7
N18	73.4	23.1	3.5	58.0	37.3	4.7	95.7	3.6	0.7
NC	69.0	27.1	3.8	51.9	43.0	5.2	95.8	3.6	0.7
Reference	97.0	2.3	0.7	96.7	2.4	0.9	96.9	2.4	0.8

Subvisible Particles

[0201] Subvisible particle levels were measured at T0 after four weeks of storage at 40°C and three freeze-thaw cycles. Table 26 shows the subvisible particle analysis for samples stored at 40°C / 75% r.h. Table 27 shows results from the freeze-thaw stress test. Most formulation variants showed favorable particle levels according to USP 788-particulate matter in injection standard. For formulation variant N12 (90 mM arginine, 135 mM trehalose, pH 6.2), an increase over the entire particle size range was seen after freeze-thaw. An increase in particle level was seen for N8 and N16 after storage at 40°C for four weeks, even though at a lower level than seen for N12 after freeze-thaw stress.

Table 26: Subvisible particle levels for size range for $\geq 5 \mu\text{m}$, $\geq 10 \mu\text{m}$ and $\geq 25 \mu\text{m}$ before (T0) and after storage at 40°C / 75% r.h.

Sample	Particle per mL $\geq 5 \mu\text{m}$	Particle per mL $\geq 10 \mu\text{m}$	Particle per mL $\geq 25 \mu\text{m}$
N1_T0	943	159	9
N2_T0	831	196	9
N3_T0	3,077	514	215
N4_T0	1,009	402	75
N5_T0	299	75	37
N6_T0	2,840	56	19
N7_T0	560	149	28
N8_T0	1,485	262	47
N9_T0	607	93	9
N10_T0	3,335	121	47
N11_T0	1,466	532	149
N12_T0	2,242	869	187
N13_T0	514	9	0
N14_T0	523	121	37
N15_T0	1,009	420	140
N16_T0	579	103	19
N17_T0	542	9	0
N18_T0	1,448	252	19
NC_T0	815	259	79
N1_T4w_40°C	1,860	290	28
N2_T4w_40°C	5,565	331	25
N3_T4w_40°C	1,625	346	65
N4_T4w_40°C	5,390	2,111	112
N5_T4w_40°C	2,952	243	0

Sample	Particle per mL ≥5 µm	Particle per mL ≥10 µm	Particle per mL ≥25 µm
N6_T4w_40°C	1,772	265	0
N7_T4w_40°C	1,037	121	9
N8_T4w_40°C	11,909	3,727	103
N9_T4w_40°C	1,569	234	28
N10_T4w_40°C	1,289	187	19
N11_T4w_40°C	2,401	392	56
N12_T4w_40°C	448	75	9
N13_T4w_40°C	2,158	121	0
N14_T4w_40°C	1,579	290	9
N15_T4w_40°C	607	93	19
N16_T4w_40°C	5,689	56	0
N17_T4w_40°C	2,522	589	56
N18_T4w_40°C	3,046	374	37
NC_T4w_40°C	570	19	0

Table 27: Subvisible particle levels for size range for ≥5 µm, ≥10 µm and ≥25 µm after freeze-thaw stress.

Sample	Particle per mL ≥5 µm	Particle per mL ≥10 µm	Particle per mL ≥25 µm
N1_T-FT	4,568	953	149
N2_T-FT	1,840	149	0
N3_T-FT	2,737	720	75
N4_T-FT	2,625	299	0
N5_T-FT	1,691	187	19
N6_T-FT	3,511	504	0
N7_T-FT	308	9	9
N8_T-FT	177	75	9
N9_T-FT	1,495	196	28
N10_T-FT	5,409	859	112
N11_T-FT	2,185	392	19
N12_T-FT	36,954	15,348	2,008
N13_T-FT	2,205	691	140
N14_T-FT	4,275	583	23
N15_T-FT	1,346	168	34
N16_T-FT	2,578	448	84
N17_T-FT	8,818	3,942	663
N18_T-FT	3,634	467	19
NC_T-FT	5,509	411	47

Fragmentation

[0202] Potential fragmentation was assessed by CGE. Samples were analyzed after T0, four weeks stored at 50°C and after three repetitive freeze thaw cycles (3x-T-FT) under non-reducing conditions. All samples were subjected to stress conditions with a similar purity between 92.5% and 93.1%, which is within method variability. After freeze-thaw stress, purity of all samples remained unchanged (Table 28 and Table 29). The highest drop in purity was noticed for formulation N14 after four weeks of storage at 50°C.

Table 28: Summarized non-reduced CGE results [%] of T0 and T4w 40°C samples reported in time corrected relative areas for IgG, Peak b, sum of HMW and sum of LMW.

Sample	Rel. TCA IgG [%]	Rel. TCA Peak b [%]	Rel. TCA Σ (HMW) [%]	Rel. TCA Σ (LMW) [%]
N1_T0	93.1	2.4	1.0	3.5
N2_T0	93.1	2.5	1.0	3.4
N3_T0	93.0	2.6	0.9	3.5
N4_T0	93.1	2.6	0.9	3.4
N5_T0	92.9	2.6	1.0	3.5
N6_T0	92.9	2.6	1.0	3.5
N7_T0	93.0	2.6	1.0	3.4
N8_T0	92.7	2.6	1.2	3.5
N9_T0	92.5	2.6	1.3	3.6
N10_T0	93.0	2.6	0.9	3.5
N11_T0	92.8	2.6	1.2	3.5
N12_T0	92.6	2.8	1.0	3.6
N13_T0	92.9	2.7	0.9	3.5
N14_T0	92.2	2.8	1.3	3.7
N15_T0	92.8	2.6	1.2	3.5
N16_T0	92.8	2.6	1.1	3.5
N17_T0	92.8	2.6	1.1	3.5
N18_T0	92.8	2.6	1.3	3.4
NC_T0	92.7	2.7	1.1	3.6
Reference, T0 n=5	93.3 $\pm$ 0.1	2.4 $\pm$ 0.1	0.7 $\pm$ 0.1	3.5 $\pm$ 0.1
N1_T4w_50°C	83.4	2.5	3.6	10.5
N2_T4w_50°C	85.4	2.4	3.2	9.0
N3_T4w_50°C	86.0	1.6	2.8	9.6
N4_T4w_50°C	85.5	1.8	2.7	10.0
N5_T4w_50°C	85.2	2.0	3.2	9.7
N6_T4w_50°C	85.7	2.3	2.7	9.4
N7_T4w_50°C	86.3	2.1	2.6	9.0
N8_T4w_50°C	85.2	2.7	3.4	8.6
N9_T4w_50°C	84.4	2.6	3.2	9.8

Sample	Rel. TCA IgG [%]	Rel. TCA Peak b [%]	Rel. TCA Σ (HMW) [%]	Rel. TCA Σ (LMW) [%]
N10_T4w_50°C	85.7	2.3	2.5	9.5
N11_T4w_50°C	84.5	3.0	3.5	9.0
N12_T4w_50°C	84.5	2.7	2.7	10.0
N13_T4w_50°C	84.9	2.6	2.6	9.9
N14_T4w_50°C	81.7	3.4	3.6	11.3
N15_T4w_50°C	83.8	3.3	3.1	9.9
N16_T4w_50°C	82.9	2.9	3.3	11.0
N17_T4w_50°C	85.0	2.6	2.9	9.5
N18_T4w_50°C	84.9	2.5	2.8	9.7
NC_T4w_50°C	84.6	2.5	2.3	10.6
Reference, n=2	92.7	2.9	0.7	3.8

Table 29: Summarized non-reduced CGE results [%] of 3xT-FT (3x freeze-thaw) samples reported in time corrected relative areas for IgG, Peak b, sum of HMW and sum of LMW.

Sample	Rel. TCA IgG [%]	Rel. TCA Peak b [%]	Rel. TCA Σ (HMW) [%]	Rel. TCA Σ (LMW) [%]
N1_T-FT	92.6	2.6	1.2	3.7
N2_T-FT	92.6	2.6	1.1	3.8
N3_T-FT	92.1	2.7	1.6	3.6
N4_T-FT	92.4	2.8	1.1	3.8
N5_T-FT	91.8	2.8	1.8	3.7
N6_T-FT	92.3	2.7	1.0	3.9
N7_T-FT	91.8	2.7	1.9	3.6
N8_T-FT	92.6	2.7	1.1	3.7
N9_T-FT	92.0	2.8	1.4	3.8
N10_T-FT	92.7	2.8	0.9	3.6
N11_T-FT	92.7	2.6	1.1	3.5
N12_T-FT	92.7	2.8	1.0	3.5
N13_T-FT	92.4	2.9	0.9	3.9
N14_T-FT	92.0	3.0	1.0	4.0
N15_T-FT	91.9	2.9	1.2	4.0
N16_T-FT	92.9	2.7	0.8	3.7
N17_T-FT	92.8	2.8	0.8	3.6
N18_T-FT	92.7	2.7	1.0	3.6
NC_T-FT	92.5	2.8	1.0	3.7
Reference, n=3	92.8 $\pm$ 0.2	2.7 $\pm$ 0.0	0.8 $\pm$ 0.1	3.7 $\pm$ 0.1

Charge Heterogeneity

[0203] Charge heterogeneity was assessed by CZE. Table 30 lists relative main charged species, Table 31 lists basic charged peak group, and Table 32 lists acidic charged peak group determined at T0 and indicated stress conditions. Samples were analyzed in duplicates. Formulation buffers were injected as a control for matrix related peaks. A slight decrease of 2-3% in main charged species was observed for all samples post freeze-thaw stress.

Table 30: Main charged species measured by CZE.

ID	Main charged species by CZE [%-relative peak area]											
	T0		3 × F/T		T2w 40°C 75% r.h.		T4w 40°C 75% r.h.		T2w 50°C		T4w 50°C	
	mean	±	mean	±	mean	±	mean	±	mean	±	mean	±
N1	70.2	0.1	67.1	0.1	53.8	0.1	44.6	0.0	29.3	0.2	18.1	0.1
N2	69.6	0.1	67.0	0.0	53.5	0.1	43.6	0.1	29.1	0.3	18.6	0.1
N3	69.9	0.0	67.2	0.5	54.9	0.2	45.9	0.1	34.0	1.0	26.4	0.2
N4	69.9	0.6	67.8	0.1	55.3	0.1	46.3	0.5	34.3	0.2	25.8	0.5
N5	70.0	0.1	67.3	0.0	54.8	0.1	44.9	0.5	32.4	0.4	22.7	0.2
N6	70.2	0.0	67.0	0.4	55.9	0.4	47.0	0.3	33.5	0.0	22.5	0.2
N7	70.2	0.0	67.3	0.3	56.8	0.2	49.0	0.2	34.4	0.5	24.5	0.0
N8	70.1	0.1	67.0	0.1	55.4	0.4	45.6	0.0	31.0	0.5	20.7	0.1
N9	69.9	0.3	67.3	0.0	55.8	0.1	44.6	0.1	32.1	0.2	21.5	0.1
N10	70.1	0.1	67.7	0.1	56.8	0.1	48.5	0.1	34.0	0.2	24.0	0.0
N11	69.7	0.1	66.5	0.6	54.6	0.1	45.6	0.0	30.7	0.3	20.5	0.1
N12	69.9	0.1	67.6	0.1	56.5	0.1	47.5	0.0	34.8	0.2	23.9	0.1
N13	69.6	0.0	67.8	0.1	56.4	0.1	47.2	0.1	36.2	1.4	24.6	0.2
N14	69.6	0.4	65.8	0.8	54.1	0.2	43.7	0.2	31.2	0.1	20.4	0.0
N15	69.3	0.3	66.4	0.8	54.9	0.2	44.8	0.2	30.3	0.5	21.2	0.0
N16	69.8	0.1	67.9	0.2	54.9	0.5	46.4	0.0	30.5	0.0	21.4	0.5
N17	69.8	0.0	67.7	0.0	52.2	0.1	45.7	0.0	30.1	0.3	20.7	0.3
N18	69.2	0.2	67.4	0.1	54.3	0.4	45.4	1.1	30.1	0.5	21.1	0.2
NC	69.8	0.1	67.2	0.0	54.7	0.2	46.1	0.4	31.6	0.3	23.3	0.1

[0204] Overall, the lowest change in decrease of main charged peak species was seen for top three formulation candidates N3, N4 and N13 after storage at elevated temperatures for four weeks at 50°C. All three formulations included 90 mM arginine, which appeared to prevent

formation of acidic charged species (Table 32) accompanied by a higher main charged species after for weeks of storage at 50°C.

Table 31: Basic charged peak group measured by CZE.

ID	Basic charged species by CZE [%-relative peak area]											
	T0		3 × F/T		T2w 40°C/75% r.h.		T4w 40°C/75% r.h.		T2w at 50°C		T4w at 50°C	
	mean	±	mean	±	mean	±	mean	±	mean	±	mean	±
N1	5.8	0.1	5.4	0.1	8.2	0.1	7.4	0.1	8.4	0.1	6.2	0.1
N2	5.4	0.1	5.2	0.0	7.9	0.1	7.1	0.1	8.1	0.1	6.4	0.0
N3	5.7	0.1	5.3	0.1	9.0	0.2	8.5	0.2	10.0	0.0	8.2	0.4
N4	6.0	0.4	5.5	0.1	9.3	0.0	8.7	0.0	10.1	0.0	9.1	0.0
N5	5.5	0.2	5.4	0.0	8.9	0.0	8.1	0.0	9.4	0.4	7.9	0.3
N6	5.4	0.0	5.1	0.0	8.5	0.1	7.5	0.1	8.8	0.0	6.7	0.1
N7	5.5	0.1	5.2	0.1	8.3	0.1	7.5	0.2	8.8	0.1	7.2	0.0
N8	5.3	0.1	5.3	0.2	7.4	0.1	6.2	0.0	6.4	0.1	5.0	0.0
N9	5.5	0.1	5.1	0.1	7.7	0.0	6.2	0.0	7.1	0.1	5.6	0.0
N10	5.5	0.0	5.2	0.1	7.8	0.0	6.8	0.0	7.7	0.0	5.9	0.0
N11	5.3	0.1	5.0	0.0	6.7	0.1	5.2	0.1	5.4	0.2	3.9	0.1
N12	5.4	0.0	5.1	0.0	7.5	0.0	5.6	0.2	6.6	0.0	5.1	0.0
N13	5.1	0.0	5.0	0.1	7.4	0.0	5.8	0.1	6.6	0.1	5.3	0.1
N14	5.1	0.1	5.0	0.1	7.3	0.0	5.3	0.2	5.9	0.1	4.5	0.0
N15	5.0	0.1	4.9	0.0	6.6	0.1	5.0	0.2	5.3	0.1	3.4	0.0
N16	5.2	0.0	5.1	0.0	7.3	0.0	6.3	0.0	7.5	0.1	5.8	0.2
N17	5.2	0.1	5.0	0.0	8.0	0.0	5.7	0.0	7.5	0.1	5.4	0.2
N18	6.0	0.3	4.9	0.0	7.9	0.1	5.7	0.2	7.2	0.1	5.5	0.0
NC	5.3	0.0	4.9	0.0	7.8	0.0	5.4	0.1	6.5	0.4	5.0	0.0

Table 32: Acidic charged peak group measured by CZE.

ID	Acidic charged species by CZE [%-relative peak area]											
	T0		3 × F/T		T2w 40°C/75% r.h.		T4w 40°C/75% r.h.		T2w at 50°C		T4w at 50°C	
	mean	±	mean	±	mean	±	mean	±	mean	±	mean	±
N1	24.0	0.0	27.5	0.0	38.1	0.1	47.9	0.1	62.3	0.1	75.7	0.2

ID	Acidic charged species by CZE [%-relative peak area]											
	T0		3 × F/T		T2w 40°C/75% r.h.		T4w 40°C/75% r.h.		T2w at 50°C		T4w at 50°C	
	mean	±	mean	±	mean	±	mean	±	mean	±	mean	±
N2	25.0	0.1	27.8	0.1	38.6	0.0	49.3	0.0	62.8	0.4	75.0	0.2
N3	24.4	0.1	27.5	0.6	36.1	0.4	45.7	0.3	56.0	1.0	65.4	0.2
N4	24.1	0.2	26.8	0.1	35.4	0.1	45.1	0.5	55.6	0.2	65.2	0.5
N5	24.5	0.0	27.3	0.0	36.4	0.1	47.0	0.5	58.2	0.0	69.4	0.1
N6	24.4	0.0	27.9	0.4	35.6	0.4	45.6	0.4	57.7	0.0	70.8	0.3
N7	24.3	0.1	27.5	0.5	34.9	0.1	43.5	0.4	56.8	0.6	68.3	0.0
N8	24.6	0.0	27.7	0.0	37.2	0.3	48.2	0.0	62.6	0.3	74.3	0.1
N9	24.6	0.2	27.7	0.1	36.6	0.1	49.2	0.0	60.8	0.1	73.0	0.1
N10	24.5	0.1	27.1	0.2	35.4	0.1	44.8	0.1	58.3	0.2	70.1	0.0
N11	25.0	0.0	28.5	0.6	38.7	0.0	49.2	0.1	64.0	0.1	75.6	0.0
N12	24.7	0.1	27.3	0.1	36.0	0.1	46.9	0.2	58.5	0.2	71.0	0.1
N13	25.3	0.0	27.2	0.2	36.2	0.1	47.0	0.2	57.2	1.4	70.1	0.2
N14	25.3	0.4	29.2	0.7	38.7	0.2	51.0	0.0	62.9	0.2	75.2	0.0
N15	25.7	0.2	28.8	0.7	38.5	0.3	50.2	0.4	64.4	0.4	75.4	0.0
N16	25.0	0.1	27.0	0.2	37.8	0.5	47.3	0.0	62.0	0.1	72.9	0.3
N17	25.1	0.0	27.3	0.0	39.8	0.1	48.7	0.0	62.4	0.2	73.9	0.5
N18	24.8	0.5	27.8	0.1	37.8	0.5	48.9	1.3	62.7	0.5	73.4	0.2
NC	24.9	0.1	27.9	0.0	37.5	0.3	48.5	0.3	61.9	0.1	71.8	0.1

Thermal Stability

[0205] Thermal stability was determined by nano-differential scanning fluorimetry (DSF).

Generally, higher thermal unfolding temperatures indicate a favorable buffer environment. The melting point (T_m) can be understood as a temperature where 50% of the molecule is unfolded, while the onset temperature (T_{on}) is related to the temperature at which the unfolding begins.

Melting temperatures above 60.0°C were achieved for all formulations (Table 33). After for weeks of storage at 40°C / 75% r.h., melting temperatures were unchanged for all formulations.

It was shown that a higher pH and a higher trehalose concentration had a significant positive impact on the T_m of felzartamab. Arginine had an adverse effect on T_m. Results are shown in

FIG. 6.

Table 33: Melting temperature (T_m) and onset temperature (T_{on}) of formulations N1-N18 and NC, at T0 and after four weeks of storage at 40°C / 75% r.h.

Formulation	T0		T4w 40°C / 75% r.h.	
	T _m [°C]	T _{on} [°C]	T _m [°C]	T _{on} [°C]
N1	65.5	59.2	65.3	58.1
N2	65.7	59.4	65.5	58.1
N3	63.6	56.6	63.5	55.1

Formulation	T0		T4w 40°C / 75% r.h.	
	T _m [°C]	T _{on} [°C]	T _m [°C]	T _{on} [°C]
N4	64.3	57.3	64.1	55.9
N5	64.1	57.3	63.9	56.3
N6	64.8	58.7	64.6	56.5
N7	64.4	57.7	64.2	56.9
N8	66.0	60.4	66.0	59.3
N9	65.3	59.2	65.2	58.1
N10	64.7	58.2	65.1	57.5
N11	66.4	60.6	66.6	59.3
N12	64.8	58.2	64.8	58.5
N13	65.2	58.9	65.3	58.9
N14	65.3	59.4	65.7	58.3
N15	66.3	60.6	66.2	59.3
N16	64.9	58.9	64.8	57.9
N17	64.9	58.9	64.7	56.1
N18	64.9	58.9	64.7	57.9
NC	65.1	58.4	64.5	56.9

Viscosity

[0206] Viscosities were determined for various formulations. **FIG. 7** shows dynamic viscosities for formulation variants N1-N18 and NC. The highest measured absolute dynamic viscosity values were obtained for arginine-free formulations (N8, N11, N15). Moreover, a lower pH (N2, pH 5.5 vs. N15, pH 6.2) reduced the dynamic viscosity substantially (8.8 mPa•s vs. 22.4 mPa•s).

Summary

[0207] To better understand potential protein-protein interactions, kD values, and the contribution of each excipient, various quality attributes were assessed at a target concentration of about 150 mg/mL. It was shown that high repulsive forces (positive charged amino acid residues) present at low pH were beneficial for protein stability. An increased arginine concentration resulted in prevention of formation of acidic charged species compromised by a reduced monomer content after four weeks of storage at 50°C. Arginine showed a two-pronged effect: (1) prevention of acidic species; and (2) increased propensity for loss of monomer content upon storage (**FIGs. 8A-8D**).

[0208] As a second factor, the contribution of pH was analyzed. pH was identified as a main modulator of viscosity. Increasing pH contributed towards increasing viscosity, with a higher tendency for formation of acidic charged species upon storage. A reduction in pH from 6.2 to 5.5 lowered viscosity by up to 250% to a value of around 10 mPa•s.

[0209] The impact of lowering pH on viscosity was higher compared to a potential beneficial effect of arginine as a viscosity reducer (10% viscosity reduction at 90 mM arginine). Contrary to the positive effect of arginine on viscosity and prevention of acidic charges species, arginine concentration was correlated to increased high molecular weight (HMW) species up to a concentration of 60 mM. Higher pH did not result in a higher monomer content after four weeks of storage at 50°C (see also **FIGs. 9A-9D**).

[0210] For trehalose, it was shown that formation of aggregates was reduced by increasing trehalose concentration. Viscosity and charged species were not affected by trehalose concentration (**FIGs. 10A-10D**).

[0211] In conclusion, 10 mM histidine, 240 mM trehalose, 0.1% (v/v) PS20, pH 5.5 was chosen as a benchmark formulation for long-term stability assessment.

Example 5: Long-term stability of candidate formulations (6 months)

[0212] Formulation candidates that were subjected to long-term stability at three storage temperatures up to six months are listed in Table 34. Methionine was added in FC2, FC4, and FC6 as a potential scavenger against potential tungsten-induced particle formation in pre-filled syringes. The vials were stored inverted to enable contact of the liquid phase with siliconized rubber stopper to simulate storage of the formulation in a prefilled syringe or cartridge application because of the siliconized interior of the barrel in the container. Storage conditions and analytical time points are shown in Table 35.

Table 34: Formulation candidates for long-term stability study

Label ID	Nominal concentration [mg/mL]	Formulation buffer
FC1	148.4	10 mM His/HCl, 240 mM trehalose, 0.1% (w/v) PS20, pH 5.5
FC2	146.9	10 mM His/HCl, 240 mM trehalose, 10 mM methionine, 0.1% (w/v) PS20, pH 5.5
FC3	148.4	10 mM His/HCl, 240 mM trehalose, 0.5% (w/v) poloxamer 188, pH 5.5
FC4	142.6	10 mM His/HCl, 240 mM trehalose, 10 mM methionine, 0.5% (w/v) poloxamer 188, pH 5.5
FC5	149.7	10 mM His/HCl, 260 mM sucrose, 0.1% PS20 (w/v), pH 6.0
FC6	146.4	10 mM His/HCl, 260 mM sucrose, 10 mM methionine, 0.1% (w/v) PS20, pH 6.0

Table 35: Storage conditions and testing time points

Storage temperature	5°C ± 3°C	25°C ± 2°C	40°C ± 2°C
Vial position	inverted	inverted	inverted
Relative humidity	Not controlled	60% ± 5%	75% ± 5%
Time points [months]	0, 3, 6, 9, 12, 18, 24, 36	0, 1, 2, 3, 6	0, 0.5, 1, 2

Analytical methods

[0213] Table 36 list the analytical methods performed for long-term stability analysis.

Table 36: Analytical methods for long-term stability

Parameter	Method
Aggregation	SEC-UPLC
Purity	CGE reducing
Fragmentation	CGE non-reducing
Heterogeneity (charge variants)	cIEF
Activity (target binding)	CD38 binding ELISA
Post translational modifications	Peptide mapping MS
Content (OD280)	UV-Scan (OD280)
pH	Potentiometry
Osmolality	Freezing point depression
Appearance of solution (color)	Visual inspection
Appearance of solution (clarity/opalescence)	Nephelometry
Visible particles	Visual inspection
Sub-visible particles	MFI

Results and Summary:Monomer Content

[0214] SEC-UPLC results are summarized in Table 37 to Table 39. For formulation candidates stored for 6 months under refrigerated conditions, no changes in monomer content were seen. For storage upon stress conditions at 40°C and 75% r.h., the observed differences among the formulation candidates became more pronounced. Formulation candidates (FC2 and FC4) showed reduced aggregation (ΔT_0 -T4w 6.9% and 7.0% monomer, respectively) among all other candidates. Methionine appeared to have a protective effect with respect to aggregation (FC1 vs. FC2 & FC3, FC4 vs. FC5 & FC6). **FIGs. 11A-11C** illustrates obtained monomer content as a function of time and storage temperature.

Table 37: SEC-UPLC results for FC1-FC6 at 5°C up to 3 and 6 months.

Formulation candidate	Relative peak area [%]					
	T0		T3M 5°C		T6M 5°C	
	HMW	Monomer	HMW	Monomer	HMW	Monomer
FC1	3.2	96.5	3.2	96.3	3.4	96.3
FC2	3.1	96.6	3.2	96.4	3.3	96.4
FC3	3.2	96.5	3.3	96.3	3.4	96.3
FC4	3.1	96.6	3.1	96.4	3.3	96.4
FC5	3.7	96.0	3.7	95.8	3.8	95.8
FC6	3.5	96.2	3.6	96.0	3.7	96.0

Table 38: SEC-UPLC results for FC1-FC6 at 25°C / 60% r.h. up to 6 months.

ID	Relative peak area [%]											
	T0			T1M 25°C			T2M 25°C			T3M 25°C		
	HMW	Monomer		HMW	Monomer		HMW	Monomer		HMW	Monomer	
FC1	3.2	96.5		3.6	96.0		3.8	95.7		4.0	95.3	
FC2	3.1	96.6		3.4	96.1		3.6	95.9		3.8	95.5	
FC3	3.2	96.5		3.6	96.0		3.9	95.7		4.1	95.2	
FC4	3.1	96.6		3.4	96.2		3.6	95.9		3.8	95.5	
FC5	3.7	96.0		4.0	95.5		4.4	95.2		4.5	94.7	
FC6	3.5	96.2		3.8	95.7		4.1	95.5		4.2	95.2	
										4.5	93.2	

Table 39: SEC-UPLC results for FC1-FC6 at 40°C / 75% r.h. up to 2 months.

Formulation candidate	Relative peak area [%]											
	T0			T0.5M 40°C			T1M 40°C			T2M 40°C		
	HMW	Monomer		HMW	Monomer		HMW	Monomer		HMW	Monomer	
FC1	3.2	96.5		4.3	93.8		5.2	91.6		6.9	88.4	
FC2	3.1	96.6		4.0	94.2		4.6	92.3		5.7	89.7	
FC3	3.2	96.5		4.4	93.7		5.4	91.5		7.5	87.9	
FC4	3.1	96.6		4.0	94.2		4.6	92.3		5.8	89.6	
FC5	3.7	96.0		4.9	93.2		5.9	91.0		7.9	87.6	
FC6	3.5	96.2		4.5	93.7		5.1	91.9		6.3	89.2	

Capillary Gel Electrophoresis

[0215] CGE was performed under non-reducing and reducing conditions for identification of potential fragmentation. Results for non-reducing conditions are summarized in Table 40 to Table 42. Results obtained under reducing conditions are shown in Table 43 to Table 45. After six months of storage at 5°C, no changes in main peak purity or altered level of fragmentation were seen among the six tested formulation candidates. After 2 months at 40°C, a decrease in main peak purity was seen for all formulation candidates, which was associated with an increase in LMW species, whereas relative peak area of Peak b remained unchanged. The lowest increase in LMW species was seen for FC2 (+3.2%). The highest increase of LMW species was observed for FC5 (+4.4%). Methionine showed a protective effect against fragmentation for polysorbate-containing formulations (compare FC1 vs. FC2 and FC5 vs. FC6). However, this effect was not observed for PX188 containing formulation (FC3 vs. FC4).

Table 40: Relative peak areas of main peak (MP), LMW species, and peak b under non-reducing conditions determined by CGE at 5°C for up to six months.

Formulation candidate	Relative peak area [%]								
	T0			T3M 5°C			T6M 5°C		
	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b
FC1	92.1	7.3	3.5	91.8	7.2	3.4	92.3	6.7	3.2
FC2	91.8	7.6	3.4	92.1	7.1	3.2	92.2	6.8	3.3
FC3	91.8	7.4	3.4	92.1	7.2	3.4	91.7	7.2	3.5
FC4	92.2	7.2	3.5	91.9	7.3	3.4	91.8	7.2	3.5
FC5	91.6	7.2	3.4	92.0	7.0	3.4	92.5	7.0	3.3
FC6	91.7	7.3	3.4	92.0	7.1	3.4	92.3	6.7	3.2

Table 41: Relative peak areas of main peak (MP), LMW species, and peak b under non-reducing conditions determined by CGE at 25°C for up to six months.

	Relative peak area [%]														
	T0			T1M 25 °C			T2M 25 °C			T3M 25 °C			T6M 25 °C		
	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b
FC1	92.1	7.3	3.5	91.1	8.1	3.7	91.5	7.4	3.4	91.1	7.6	3.6	90.4	7.8	3.3
FC2	91.8	7.6	3.4	91.3	8.0	3.6	91.8	7.3	3.3	91.3	7.5	3.4	90.6	7.7	3.3

	Relative peak area [%]														
	T0			T1M 25 °C			T2M 25 °C			T3M 25 °C			T6M 25 °C		
	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b
FC3	91.8	7.4	3.4	91.0	8.2	3.6	91.4	7.3	3.4	91.1	7.6	3.4	90.9	7.5	3.3
FC4	92.2	7.2	3.5	91.4	8.0	3.6	91.7	7.2	3.2	91.3	7.5	3.3	91.0	7.6	3.3
FC5	91.6	7.2	3.4	91.4	7.7	3.6	91.1	7.3	3.3	90.5	7.7	3.5	90.2	7.9	3.3
FC6	91.7	7.3	3.4	91.7	7.7	3.6	91.6	6.9	3.1	91.2	7.3	3.3	90.6	7.5	3.2

Table 42: Relative peak areas of main peak (MP), LMW species and peak b under non-reducing conditions determined by CGE at 40°C for up to two months.

Formulation candidate	Relative peak area [%]											
	T0			T0.5M 40°C			T1M 40°C			T2M 40°C		
	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b	MP	LMW	peak b
FC1	92.1	7.3	3.5	91.0	7.9	3.3	88.7	9.7	3.8	86.7	11.2	3.2
FC2	91.8	7.6	3.4	91.3	7.5	3.3	89.1	9.5	3.8	87.4	10.8	3.2
FC3	91.8	7.4	3.4	90.8	7.8	3.4	88.8	9.4	3.7	86.8	10.8	3.2
FC4	92.2	7.2	3.5	91.1	7.6	3.3	88.7	9.8	3.7	87.3	11.0	3.1
FC5	91.6	7.2	3.4	90.4	7.9	3.4	88.1	10.0	3.9	85.6	11.7	3.7
FC6	91.7	7.3	3.4	91.3	7.4	3.4	88.1	9.9	4.0	86.9	11.0	3.7

Table 43: Relative peak areas of summed heavy and light chain (HC+LC) and sum of non-glycosylated HC (NG-HC) determined by CGE under reducing conditions for storage up to 6 months at 5°C.

Formulation candidate	Relative peak area [%]					
	T0		T3M 5°C		T6M 5°C	
	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC
FC1	97.4	1.1	97.4	1.1	97.4	1.1
FC2	97.5	1.1	97.4	1.1	97.5	1.1
FC3	97.6	1.1	97.4	1.1	97.6	
FC4	97.7	1.1	97.4	1.1	97.3	1.1
FC5	97.5	1.1	97.4	1.1	97.5	1.1
FC6	97.6	1.1	97.4	1.1	97.1	1.2

Table 44: Relative peak areas of summed heavy and light chain (HC+LC) and sum of non-glycosylated HC (NG-HC) determined by CGE under reducing conditions for storage up to 6 months at 25°C.

	Relative peak area [%]									
	T0		T1M 25°C		T2M 25°C		T3m 25°C		T6M 25°C	
	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC
FC1	97.4	1.1	97.5	1.1	96.9	1.1	96.8	1.1	96.4	1.1
FC2	97.5	1.1	97.5	1.1	97.1	1.1	97.0	1.1	96.5	1.1
FC3	97.6	1.1	97.4	1.1	96.6	1.1	97.1	1.1	96.6	1.1
FC4	97.7	1.1	97.6	1.2	97.0	1.1	97.0	1.1	96.7	1.1
FC5	97.5	1.1	97.2	1.1	96.8	1.1	96.7	1.1	96.2	1.2
FC6	97.6	1.1	97.3	1.1	96.6	1.2	96.9	1.1	96.1	1.2

Table 45: Relative peak areas of summed heavy and light chain (HC+LC) and sum of non-glycosylated HC (NG-HC) determined by CGE under reducing conditions for storage up to 2 months at 40°C.

	Relative peak area [%]							
	T0		T0.5M 40°C		T1M 40°C		T2M 40°C	
	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC	HC+LC	NG+HC
FC1	97.4	1.1	97.0	1.1	96.2	1.1	94.3	1.2
FC2	97.5	1.1	97.0	1.1	96.3	1.2	94.5	1.2
FC3	97.6	1.1	97.0	1.1	96.2	1.1	94.1	1.2
FC4	97.7	1.1	97.2	1.2	96.1	1.2	94.2	1.2
FC5	97.5	1.1	96.7	1.1	95.6	1.2	93.4	1.2
FC6	97.6	1.1	96.9	1.1	95.7	1.2	93.3	1.3

Capillary Isoelectric Focusing (cIEF)

[0216] For tracking of chemical changes, charge variants capillary isoelectric focusing was performed. Results were recorded as relative main peak (MP) area, acidic peak (AP) group, and basic peak (BP) group (Table 46 to Table 48). All formulation candidates were characterized by an increase in acidic peak group accompanied by a decrease in main peak after storage at 40°C over the course of two months. Basic peak group remained unchanged. The observed differences among the formulation candidates were similar with respect to chemical changes.

Table 46: Relative peak areas determined by cIEF for samples stored at 5°C over six months.

Formulation candidate	Relative peak area [%]								
	T0			T3M 5°C			T6M 5°C		
	MP	AP	BP	MP	AP	BP	MP	AP	BP
FC1	73.3	21.2	5.5	75.1	19.9	5.0	75.7	19.4	4.9
FC2	73.2	21.2	5.6	75.2	20.0	4.9	75.8	19.0	5.2
FC3	73.3	21.2	5.5	75.4	19.9	4.8	75.6	19.3	5.1
FC4	73.8	20.9	5.3	75.4	19.5	5.2	75.8	19.4	4.8
FC5	74.6	20.4	5.0	74.6	20.6	4.8	75.2	20.0	4.7
FC6	73.0	21.3	5.6	74.6	20.5	4.9	74.6	20.2	5.2

Table 47: Relative peak areas determined by cIEF for samples stored at 25°C / 60% r.h over six months.

Formulation candidate	Relative peak area [%]														
	T0			T1M 25°C			T2M 25°C			T3M 25°C			T6M 25°C		
	MP	AP	BP	MP	AP	BP	MP	AP	BP	MP	AP	BP	MP	AP	BP
FC1	73.3	21.2	5.5	72.7	21.8	5.5	69.5	24.8	5.7	66.7	27.2	6.1	60.8	32.6	6.6
FC2	73.2	21.2	5.6	72.9	21.6	5.6	69.8	24.5	5.7	67.4	26.7	5.9	60.7	32.7	6.6
FC3	73.3	21.2	5.5	72.8	21.6	5.6	69.3	24.9	5.8	67.4	27.0	5.6	60.8	32.5	6.7
FC4	73.8	20.9	5.3	72.3	22.0	5.8	69.7	24.5	5.8	67.6	26.6	5.8	61.5	31.9	6.5
FC5	74.6	20.4	5.0	72.4	22.5	5.1	69.7	25.1	5.2	67.2	27.7	5.2	62.5	32.2	5.2
FC6	73.0	21.3	5.6	72.3	22.6	5.1	70.1	24.7	5.2	67.9	27.3	4.8	62.5	32.2	5.4

Table 48: Relative peak areas determined by cIEF for samples stored at 40°C / 75% r.h. over the course of two months.

Formulation candidate	Relative peak area [%]											
	T0			T0.5M 40°C			T1M 40°C			T2M 40°C		
	MP	AP	BP	MP	AP	BP	MP	AP	BP	MP	AP	BP
FC1	73.3	21.2	5.5	62.8	30.4	6.8	50.0	43.1	6.9	36.9	57.0	6.1
FC2	73.2	21.2	5.6	63.2	30.2	6.6	51.2	42.3	6.6	37.9	56.4	5.7
FC3	73.3	21.2	5.5	62.8	30.6	6.6	50.8	42.4	6.8	36.7	57.3	5.9
FC4	73.8	20.9	5.3	62.9	30.3	6.8	50.9	42.2	6.9	37.7	56.6	5.7
FC5	74.6	20.4	5.0	63.1	30.9	6.0	52.6	42.1	5.3	38.6	57.0	4.4
FC6	73.0	21.3	5.6	64.4	29.3	6.3	52.5	42.0	5.6	39.8	56.4	5.3

Binding Activity (CD38 ELISA)

[0217] Felzartamab binding to CD38 was assessed by CD38 ELISA. The results are shown in Table 49 as relative activity compared to reference. No substantial changes in CD38 binding activity were seen for any of the formulation candidates.

Table 49: CD38 binding ELISA activity relative to reference as a function of storage time and temperature

Formulation candidate	CD38 binding ELISA % relative to reference									
Time	T0	T3M	T6M	T1M	T2M	T3M	T6M	T0.5M	T1M	T2M
Storage temperature	5°C			25°C / 60% r.h.				40°C / 75% r.h.		
FC1	96	88	94	99	96	96	94	87	81	89
FC2	79	93	98	101	113	98	92	100	90	90
FC3	88	96	100	94	99	85	100	105	89	85
FC4	103	96	96	88	105	83	89	101	101	96
FC5	95	113	99	82	85	94	88	92	92	90
FC6	94	92	90	89	88	90	88	98	93	87

Concentration, pH and Osmolality

[0218] All determined protein concentrations were within $\pm 3\%$ range in comparison to the initial determined T0 value. A 6% decrease in content was noticed only for FC6, which was stored for two months at 40°C / 75% r.h. Further, no changes in pH or osmolality were seen for any of the formulation candidates FC1 to FC6.

Micro-Flow Imaging

[0219] Sub-visible particle levels were assessed by micro-flow imaging (MFI) measurements. Results for formulations stored at 5°C are shown in Table 50 and **FIGs. 12A-12B**. Formulation candidates FC5 and FC6 contained more sub-visible particles across all size ranges as compared to pH 5.5 trehalose candidates (FC1-FC4) if subjected to storage temperatures above 25°C.

Table 50: Sub-visible particle level for formulation candidates stored at 5°C for up to six months.

ID	Sub-visible particle concentration [#/mL]								
	T0			T3M 5 °C			T6M 5 °C		
	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm
FC1	426	24	7	12,475	615	67	7,511	245	13
FC2	404	14	1	1,551	43	1	2,630	212	4
FC3	1,446	50	6	957	86	4	1,283	79	10
FC4	700	38	4	347	33	7	683	60	23
FC5	247	6	0	275	10	4	1,017	19	2
FC6	366	16	2	438	26	12	871	42	4

Table 51: Sub-visible particle level for formulation candidates stored at 25°C for up to six months.

ID	Sub-visible particle concentration [# per mL]														
	T0			T1M 25°C			T2M 25°C			T3M 25°C			T6M 25°C		
	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm
FC1	426	24	7	1,073	54	12	4,149	327	20	1,554	60	4	12,631	324	18
FC2	404	14	1	640	36	12	3,195	167	9	1,812	73	7	11,135	320	16
FC3	1,446	50	6	2,051	153	12	1,385	193	36	2,007	135	30	1,231	141	20
FC4	700	38	4	657	58	12	1,505	164	24	1,122	90	17	1,071	129	21
FC5	247	6	0	1,273	60	12	3,753	266	9	2,441	1635	2,261	19,253	361	8
FC6	366	16	2	2,049	51	12	2,111	151	12	3,766	80	8	15,601	337	7

Table 52: Sub-visible particle level for formulation candidates stored at 40°C for up to two months.

Formulation candidate	Sub-visible particle concentration [# /ml]											
	T0			T0.5M 40°C			T1M 40°C			T2M 40°C		
	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm	≥2 µm	≥10 µm	≥25 µm
FC1	426	24	7	329	20	3	707	70	10	2,461	215	36
FC2	404	14	1	603	13	2	768	56	5	1,783	166	26
FC3	1,446	50	6	459	31	4	744	82	14	1,060	104	27
FC4	700	38	4	857	92	24	286	32	4	1,658	213	37
FC5	247	6	0	518	20	1	1222	50	5	6,364	470	59
FC6	366	16	2	1,284	25	1	2359	95	7	13,420	686	65

[0220] Sample color was assessed on a Brown/Yellow (BY) scale (BY1-BY7). All formulation candidates stored at 5°C over the course of six months were rated with $\leq$ BY6. For storage at 25°C and 40°C, results are summarized in Table 53. After storage of two months, formulations FC5 and FC6 showed a change from BY6 to BY5, which was also seen for all formulations after storage at 40°C for two months associated with an increase in nephelometric turbidity units (NTU). Formulation candidate FC4 remained unchanged in color after six months of storage at 25°C. The smallest changes in clarity were noticed for FC4, where clarity remained practically unchanged irrespective of storage condition and temperature.

Table 53: Color of formulation candidates as a function of storage time and temperature.

Formulation candidate	Color (BY scale)							
Storage time	T0	T0.5M	T1M		T2M		T3M	T6M
Temperature	-	40°C	25°C	40°C	25°C	40°C	25°C	25°C
FC1	< BY6	< BY6	< BY6	< BY6	< BY6	< BY5	< BY6	< BY5
FC2	< BY6	< BY6	< BY6	< BY6	< BY6	< BY5	< BY6	< BY5
FC3	< BY6	< BY6	< BY6	< BY6	< BY6	< BY5	< BY6	< BY5
FC4	< BY6	< BY6	< BY6	< BY6	< BY6	< BY5	< BY6	< BY6
FC5	< BY6	< BY6	< BY6	< BY6	< BY5	< BY5	< BY5	< BY5
FC6	< BY6	< BY6	< BY6	< BY6	< BY5	< BY5	< BY5	< BY5

Table 54: Opalescence/clarity in NTU for six formulation candidates as a function of storage time and temperature

Formulation candidate	Opalescence in NTU									
Storage time	T0	T0.5M	T1M		T2M		T3M		T6M	
Temperature	-	40°C	25°C	40°C	25°C	40°C	5°C	25°C	5°C	25°C
FC1	6	6	6	7	6	9	7	7	7	9
FC2	6	6	6	8	6	14	6	8	7	7
FC3	6	7	6	7	6	8	6	7	7	10
FC4	6	6	6	7	6	8	6	6	7	6
FC5	8	9	8	10	9	13	8	9	9	10
FC6	8	9	8	10	9	15	8	9	9	10

[0221] The best colloidal characteristics with respect to low aggregation rate was seen for formulation candidates FC2, FC4, and FC6, which is in good agreement with non-reducing CGE

data. All formulations revealed monomer contents above 95.8% after 6 months of storage at 4-8°C. A direct head-to-head comparison on aggregation deltas of formulations stored for two months at 40°C with and without 10 mM methionine suggests a beneficial and protective effect of methionine with respect to aggregation prevention. However, formulation candidate FC6 was compromised by a remarkable increase in sub-visible particle levels after two months of storage at 40°C.

[0222] All formulation candidates were free of proteinaceous visible particles, despite FC5 exhibiting white flaky particles after storage at 40°C for up to two months. Chemical alterations were tracked by isoelectric focusing. The formation of acidic charged species was not impacted by any of the formulations. The potency of felzartamab, as assessed by CD38 ELISA, was unchanged irrespective of formulation, time, or storage temperature. Osmolality and pH were unchanged.

[0223] Overall, formulation candidates FC4 (10 mM His/HCl, 240 mM trehalose, 10 mM methionine 0.5% poloxamer 188, pH 5.5) and FC6 (10 mM His/HCl, 260 mM sucrose, 10 mM methionine, 0.1% PS20, pH 6.0) were found to surprisingly combine high colloidal stability in combination with maintenance of potency and low viscosity characteristics. The rheological attributes of those formulation are well-suited for application in prefilled syringes or similar autoinjector devices.

Example 6: Stability testing of candidate formulations

[0224] This study aims to compare potential new formulations for HIB202/MOR202 (INN: felzartamab) to enable a subcutaneous administration for future clinical and commercial application. Accordingly, the stability of the six candidate formulations at the target concentration of 150 mg/mL is compared under anticipated long-term, accelerated, and stress condition. The study will provide stability data for candidate formulations (nominal concentration: 150 mg/mL) over a storage period of 36 months at 5 °C ± 3 °C (long-term condition), over 6 months at 25 °C ± 2°C (accelerated condition), and over 8 weeks at 40 °C ± 2 °C (stress condition).

Materials

[0225] The present stability tests use six formulation candidates, FC1-FC6 (see **Table 55**, below).

Table 55: Formulations for stability testing

Label ID	Nominal concentration [mg/mL] *	Density (g/mL)	Formulation buffer
FC1**	148.4	1.062	10 mM His/HCl, 240 mM trehalose, 0.1% (w/v) PS20, pH 5.5
FC2**	146.9	1.062	10 mM His/HCl, 240 mM trehalose, 10 mM methionine, 0.1% (w/v) PS20, pH 5.5
FC3**	148.4	1.062	10 mM His/HCl, 240 mM trehalose, 0.5% (w/v) poloxamer 188, pH 5.5
FC4	142.6	1.062	10 mM His/HCl, 240 mM trehalose, 10 mM methionine, 0.5% (w/v) poloxamer 188, pH 5.5
FC5**	149.7	1.063	10 mM His/HCl, 260 mM sucrose, 0.1% PS20 (w/v), pH 6.0
FC6	146.4	1.063	10 mM His/HCl, 260 mM sucrose, 10 mM methionine, 0.1% (w/v) PS20, pH 6.0

* OD280 value from timepoint 0 to be used for all calculations.

** Last analyzed sampling point is 6 months at intended/accelerated conditions.

Remaining vials are kept at the respective temperatures until final notice to discard.

Storage Conditions

[0226] Three storage conditions are used in the current study according to **Table 56**. The vials are stored inverted to enable contact of the liquid phase with the siliconized rubber stopper as a surrogate for a potential prefilled syringe or cartridge application, which are in most cases also siliconized inside of the barrel in a container under the indicated conditions. Primary packaging materials used for storage are described in **Table 57**.

Table 56: Storage conditions and testing time points

	Long-term	Accelerated	Stress
Temperature	5 ± 3 °C	25 ± 2 °C	40 ± 2 °C
Vial Position	Inverted	Inverted	Inverted
Humidity	Not controlled	60% RH ± 5%	75% RH ± 5%

	Long-term	Accelerated	Stress
Testing Frequency	0, 3, 6, 9, 12, 18, 24, and 36 months	0, 1, 2, 3, and 6 months	0, 0.5, 1, and 2 months

Table 56: Primary packaging material used for storage

Component	Description
Vial	2R vial, 1 st hydr. class
Stopper	13 mm serum stopper, 1256/4110/40/GREY, silicone ¼ A, FluroTec (03) 0.10 black
Flip-off cap	Crimps caps, flip-off, white, yellow, red and blue

[0227] The minimum sampling requirements per each candidate formulation are shown in **Table 57**.

Table 57: Minimum sample requirements per candidate formulation

Months	0	0.5	1	2	3	6	9	12	18	24	36	Back up	Sum
Storage	Required number of vials												
5 + 3 °C	8	-	-	-	8	8	8	8	8	8	8	60*	124
25 + 2 °C		-	8	8	8	8	-	-	-	-	-	16	48
40 + 2 °C		8	8	8	-	-	-	-	-	-	-	8	32
											Total: 204		

*The number of backup vials is calculated based on the smallest amount of available vials of the different formulation candidates (*i.e.*, FC6). For all other formulation candidates more vials (up to 250) are available. These surplus vials are stored as additional back up vials at 5 ± 3°C for each formulation candidate respectively.

[0228] The sampling time points may deviate from the intended sampling time point according to **Table 58**.

Table 58: Permitted deviation in sampling time points

Storage Time	Sampling Point
≤ 3 months	+ 7 calendar days
> 3 months to < 12 months	± 14 calendar days
≥ 12 months	± 28 calendar days

Methods

[0229] Representative methods for assessing stability of candidate formulations are shown in Table 59, below.

Table 59: Analytical methods for stability testing of candidate formulations

Parameter	Method*	Data Reported
Aggregation	SEC-UPLC	% area HMW % area monomer % area LMW
Purity	CGE reducing	% Sum of HC and LC % area of HC % area LC % area sum of LMW % area sun of HMW
Fragmentation	CGE non-reducing	% area main peak % fragments (LMWs) % HMWs
Heterogeneity (charge variants)	cIEF	% sum of acid peaks % main peak % sum of basic peaks % of peak j % of peak k % of peak l % of peak n
Activity (target binding)	CD38 binding ELISA	% activity compared to reference standard

Parameter	Method*	Data Reported
Post translational modifications	Peptide mapping MS	According to method description and raw data
Content (OD280)	UV-Scan (OD280)	Concentration [mg/mL]
pH	Potentiometry	pH
Osmolality	Freezing point depression	Osmolality [mOsmol/kg]
Appearance of solution (color)	Visual inspection	Comparison to standard solutions (BY)
Appearance of solution (clarity/opalescence)	Nephelometry	Opalescent value [NTU]
Visible particles	Visual inspection	According to method description
Sub-visible particles	MFI	Particles/mL

* Summary of test methods provided in **Table 64**, below.

CGE Reduced Analysis

[0230] Due to the high protein concentration of HCLF samples, large volumes of SDS-MW sample buffer (100 mM Tris-HCl / 1.0% SDS / pH 9.0) are used for dilution of samples to the concentration as defined in the analytical method. In-house prepared SDS-MW sample buffer (pH 9.0) is used. Preparation is performed according to the following requirements. 606 mg of Tris is weighed into a suitable vessel and dissolved in about 30 mL of water. The pH is adjusted with 6 N HCl to 9.0. 500 mg SDS is dissolved in the solution. Volume is adjusted in a volumetric flask to 50 mL.

CGE Non-reduced Analysis

[0231] Due to the high protein concentration of HCLF samples, large volumes of SDS-MW sample buffer (100 mM Tris-HCl / 1.0% SDS / pH 7.2) are used for dilution of samples to the concentration as defined in the analytical method. In-house prepared SDS-MW sample buffer (pH 7.2) is used. 606 mg of Tris is weighed into a suitable vessel and dissolved in about 30 mL of water. The pH is adjusted with 6 N HCl to 7.2. 500 mg SDS is dissolved in the solution. Volume is adjusted in a volumetric flask to 50 mL.

Content (OD280) Analysis

[0232] Due to the high protein concentration of HCLF samples, a dilution factor of 200 is used. 0.05 mL of sample solution is diluted with 9.95 mL formulation buffer.

Sample Handling

[0233] The quantity of sample required for each mode of analysis is provided in **Table 60**, below.

Table 60: Sample requirements per sample point

Analytical Method	Required Number of Vials	Aliquoted/Pooled Volume
SEC-UPLC	3 Vials	250 µL
CGE Reducing		250 µL
CGE Non-reducing		250 µL
cIEF		250 µL
Peptide Mapping MS		250 µL
CD38 ELISA		2 × 250 µL
Osmolarity		250 µL
Content (OD280)		500 µL
Clarity	2 Vials	Approx. 4 mL
Color		
pH		
Visible Particles	3 Vials	N.A.
Sub-visible Particles		6 mL

[0234] For each condition at each sampling point, vials are equilibrated to room temperature and aliquoted for analytics according to **Table 60**. Respective aliquoted samples are stored frozen at < -60 °C until analysis. Frozen back-up samples aliquots may be used for repeat testing. The schedule of testing by specific analytical methods for each of the long-term (5 ± 3 °C), accelerated (25 ± 2 °C), and stress (40 ± 2 °C) conditions is shown in **Tables 61-63**, respectively.

Table 61: Testing schedule for long-term storage conditions

Analytical Method	Time (months)							
	0	3	6	9	12	18	24	36
SEC-UPLC	x	x	x	x	x	x	x	x
CGE Reducing	x	x	x	x	x	x	x	x
CGE Non-reducing	x	x	x	x	x	x	x	x
cIEF	x	x	x	x	x	x	x	x
CD38 ELISA	x	x	x	x	x	x	x	x
Peptide Mapping MS	x	-	x	-	x	-	x	x
Content (OD280)	x	x	x	x	x	x	x	x
pH	x	x	x	x	x	x	x	x
Color	x	x	x	x	x	x	x	x
Clarity	x	x	x	x	x	x	x	x
Osmolarity	x	x	x	x	x	x	x	x
Visible Particles	x	x	x	x	x	x	x	x
Sub-visible Particles	x	x	x	x	x	x	x	x

“x” = tested;

“-” = not tested.

Table 61: Testing schedule for accelerated conditions

Analytical Method	Time (months)				
	0	1	2	3	6
SEC-UPLC	x	x	x	x	x
CGE Reducing	x	x	x	x	x
CGE Non-reducing	x	x	x	x	x
cIEF	x	x	x	x	x
CD38 ELISA	x	x	x	x	x
Peptide Mapping MS	x	-	-	x*	x
Content (OD280)	x	x	x	x	x
pH	x	x	x	x	x

Analytical Method	Time (months)				
	0	1	2	3	6
Color	x	x	x	x	x
Clarity	x	x	x	x	x
Osmolarity	x	x	x	x	x
Visible Particles	x	x	x	x	x
Sub-visible Particles	x	x	x	x	x

“x” = tested;

“-” = not tested.

*Sampling and storage performed at < 60 °C.

Table 61: Testing schedule for stress conditions

Analytical Method	Time (months)			
	0	0.5	1	2
SEC-UPLC	x	x	x	x
CGE Reducing	x	x	x	x
CGE Non-reducing	x	x	x	x
cIEF	x	x	x	x
CD38 ELISA	x	x	x	x
Peptide Mapping MS	x	-	-	x*
Content (OD280)	x	-	x	x
pH	x	x	x	x
Color	x	x	x	x
Clarity	x	x	x	x
Osmolarity	x	x	x	x
Visible Particles	x	x	x	x
Sub-visible Particles	x	x	x	x

“x” = tested;

“-” = not tested.

*Sampling and storage performed at < 60 °C.

Table 64: Summary of analytical methods used for stability testing

Analytical Method	Summary
High-Performance Size Exclusion Chromatography (SEC-UPLC)	High performance size exclusion chromatography (SEC-UPLC) separates molecules according to their molecular size. The stationary phase consists of gel-like particles with a defined pore size. Molecules larger than these pores elute first, whereas molecules smaller than these pores of the stationary phase take longer to migrate through the column and thus elute later. The detection is performed at 280 nm and the impurities (high molecular weight species and low molecular weight species) of felzartamab are determined as percentage of total area in the chromatogram
Capillary Isoelectric Focusing (cIEF)	cIEF is a mode of electrophoresis that separates protein molecules based on their pI values. The assay is based on the introduction of the protein samples into a capillary with a mixture of ampholyte buffers, which are a polymerized mixture of monomers that contain weakly acidic and weakly basic groups. By using an acidic solution on the anode side of the capillary (anolyte) and a basic solution on the cathode side (catholyte) and applying an electric field, the ampholyte molecules orient themselves with respect to their pKa value, generating a pH gradient within the capillary. Proteins then migrate through the ampholyte mixture and focus at a pH where they become electrically neutral (isoelectric point or pI). Detection of individual charge peaks occurs when the capillary is illuminated with UV at 280 nm. The charge heterogeneity can be determined by expressing the

Analytical Method	Summary
	integrated areas of the peaks as a percentage of the total integrated area in the chromatogram. For purity evaluation, the charge heterogeneity is reported as the integrated areas of the peaks as a percentage of the total integrated area in the chromatogram for main peak, sum of acidic peaks, and sum of basic peaks.
Peptide Mapping Mass Spectrometry	Post-translational modifications are analyzed by peptide mapping with both tryptic and Glu-C digestion. The digestion procedure involves drying down the test samples using a vacuum concentrator and then reconstituting them in high concentration of guanidine buffer (6.0 M guanidine hydrochloride). The samples are reduced with DTT and alkylated with sodium iodoacetate. A gel filtration column is used to desalt the samples before digestion. For trypsin digestion (1:50 w/w, enzyme/protein), the sample is digested for 2 hours. For the analysis of post-translation modifications, including the determination of the oligosaccharide species, the peptides are separated by reversed-phase HPLC using a C18 column and a gradient of acetonitrile containing trifluoroacetic acid. The chromatography is performed on an HPLC system with UV detection at 214 nm. An online LTQ linear is used in-line after the UV detector to collect mass spectra of the intact peptide as well as to fragment the peptides for sequencing (MS/MS analysis). Peak areas of selected ion chromatograms of glycosylated peptides are used to quantify each oligosaccharide species. For the percentage calculation, all detectable

Analytical Method	Summary
	oligosaccharide structures of heavy chain peptide HC_T23 (HC: 296-304) are counted. Heavy chain peptide HC_T23 of felzartamab contains the major glycosylation site at asparagine 300 (Asn 300).
pH	The pH value is determined with a calibrated pH meter. Reference solutions are used for the calibration, which span the range of pH of the sample solutions. The temperature of the sample solutions is simultaneously measured and must be in the range of 23 °C - 25 °C.
Osmolarity	The osmolality of felzartamab sample solution is determined by the measurement of the freezing point depression. Reference solutions are used for the calibration and they must span the range of osmolality of the sample solutions.
Visible Particles	Felzartamab samples are visually inspected against white background and black background with the aim to evaluate the presence of visible particles.
Sub-visible Particles	Felzartamab samples are analyzed for sub-visible particles. Thereby, the number of particles equal or greater than 10 µm and 25 µm in size are determined using a suitable apparatus based on the principle of light obscuration.

OTHER EMBODIMENTS

[0235] Various modifications and variations of the described disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure that are

obvious to those skilled in the art are intended to be within the scope of the disclosure. Other embodiments are in the claims

CLAIMS

What is claimed is:

1. A liquid pharmaceutical formulation, comprising:
 - (a) an anti-CD38 antibody or antigen-binding fragment thereof;
 - (b) a sugar;
 - (c) a non-ionic surfactant;
 - (d) a stabilizer; and
 - (e) a histidine buffer having a pH in the range of 5.0 to 7.0.
2. The liquid pharmaceutical formulation of claim 1, wherein the anti-CD38 antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising a complementarity determining region 1 (HCDR1) having the amino acid sequence of SEQ ID NO: 1, a HCDR2 having the amino acid sequence of SEQ ID NO: 2, and a HCDR3 having the amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a complementarity determining region 1 (LCDR1) having the amino acid sequence of SEQ ID NO: 4, a LCDR2 having the amino acid sequence of SEQ ID NO: 5 and a LCDR3 having the amino acid sequence of SEQ ID NO 6.
3. The liquid pharmaceutical formulation of claim 1 or 2, wherein the anti-CD38 antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO: 7 and a VL comprising the amino acid sequence of SEQ ID NO:8.
4. The liquid pharmaceutical formulation of any one of claims 1-3, wherein the anti-CD38 antibody or antigen-binding fragment thereof is felzartamab or antigen-binding fragment thereof.
5. The liquid pharmaceutical formulation of any one of claims 1-4, wherein the formulation includes the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 100 mg/mL to about 200 mg/mL.
6. The liquid pharmaceutical formulation of any one of claims 1-5, wherein the formulation includes the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL.

7. The liquid pharmaceutical formulation of any one of claims 1-6, wherein the sugar is trehalose or sucrose.
8. The liquid pharmaceutical formulation of claim 7, wherein the sugar is trehalose and is included in the formulation at a concentration in the range of about 200 to about 300 mM.
9. The liquid pharmaceutical formulation of claim 7 or 8, wherein the sugar is trehalose and is included in the formulation at a concentration of about 240 mM.
10. The liquid pharmaceutical formulation of any one of claims 1-7, wherein the sugar is sucrose and is included in the formulation at a concentration in the range of about 200 to about 300 mM.
11. The liquid pharmaceutical formulation any one of claims 1-7 or 10, wherein the sugar is sucrose and is included in the formulation at a concentration of about 260 mM.
12. The liquid pharmaceutical formulation of any one of claims 1-11, wherein the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration in the range of 0.1% (w/v) to 1.0% (w/v).
13. The liquid pharmaceutical formulation of any one of claims 1-12, wherein the non-ionic surfactant is poloxamer 188 and is included in the formulation at a concentration of 0.5% (w/v).
14. The liquid pharmaceutical formulation of any one of claims 1-11, wherein the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration in the range of 0.01% (w/v) to 1.0% (w/v).
15. The liquid pharmaceutical formulation of any one of claims 1-11 or 14, wherein the non-ionic surfactant is polysorbate 20 and is included in the formulation at a concentration of 0.1% (w/v).
16. The liquid pharmaceutical formulation of any one of claims 1-15, wherein the stabilizer is methionine and is included in the formulation at a concentration in the range of 5 mM to 20 mM.

17. The liquid pharmaceutical formulation of any one of claims 1-16, wherein the stabilizer is methionine and is included in the formulation at a concentration of 10 mM.
18. The liquid pharmaceutical formulation of any one of claims 1-17, wherein the histidine buffer is included in the formulation at a concentration in the range of 5 to 20 mM.
19. The liquid pharmaceutical formulation of any one of claims 1-18, wherein the histidine buffer is included in the formulation at a concentration of 10 mM.
20. The liquid pharmaceutical formulation of any one of claims 1-19, wherein the histidine buffer has a pH of about 5.5 to about 6.0.
21. The liquid pharmaceutical formulation of any one of claims 1-20, wherein the histidine buffer has a pH of about 5.5.
22. The liquid pharmaceutical formulation of any one of claims 1-21, wherein the histidine buffer has a pH of about 6.0.
23. The liquid formulation of any one of claims 1-7, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
 - (b) trehalose at a concentration of about 240 mM;
 - (c) methionine at a concentration of about 10 mM;
 - (d) poloxamer 188 at a concentration of about 0.5% (w/v); and
 - (e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.
24. The liquid formulation of any one of claims 1-7 or 23, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) trehalose at a concentration of 240 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) poloxamer 188 at a concentration of 0.5% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.

25. The liquid formulation of any one of claims 1-7, 23, or 24, consisting of:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) trehalose at a concentration of 240 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) poloxamer 188 at a concentration of 0.5% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of 5.5.
26. The liquid formulation of any one of claims 1-7, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
 - (b) sucrose at a concentration of about 260 mM;
 - (c) methionine at a concentration of about 10 mM;
 - (d) polysorbate 20 at a concentration of about 0.1% (w/v); and
 - (e) histidine buffer at a concentration of about 10 mM and having a pH of about 6.0.
27. The liquid formulation of any one of claims 1-7 or 26, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) sucrose at a concentration of 260 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) polysorbate 20 at a concentration of 0.1% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.
28. The liquid formulation of any one of claims 1-7, 26, or 27, consisting of:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) sucrose at a concentration of 260 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) polysorbate 20 at a concentration of 0.1% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of 6.0.

29. The liquid formulation of any one of claims 1-8, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
 - (b) trehalose at a concentration of about 240 mM;
 - (c) methionine at a concentration of about 10 mM;
 - (d) polysorbate 20 at a concentration of about 0.1% (w/v); and
 - (e) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.
30. The liquid formulation of any one of claims 1-8 or 29, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) trehalose at a concentration of 240 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) polysorbate 20 at a concentration of 0.1% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of about 5.5.
31. The liquid formulation of any one of claims 1-8, 29, or 30, consisting of:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) trehalose at a concentration of 240 mM;
 - (c) methionine at a concentration of 10 mM;
 - (d) polysorbate 20 at a concentration of 0.1% (w/v); and
 - (e) histidine buffer at a concentration of 10 mM and having a pH of about 5.5.F
32. The liquid formulation of any one of claims 1-7, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of about 150 mg/mL;
 - (b) trehalose at a concentration of about 240 mM;
 - (c) poloxamer 188 at a concentration of about 0.5% (w/v); and
 - (d) histidine buffer at a concentration of about 10 mM and having a pH of about 5.5.
33. The liquid formulation of any one of claims 1-7 or 32, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;

- (b) trehalose at a concentration of 240 mM;
 - (c) poloxamer 188 at a concentration of 0.5% (w/v); and
 - (d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.
34. The liquid formulation of any one of claims 1-7, 32 or 33, comprising:
- (a) the anti-CD38 antibody or antigen-binding fragment thereof at a concentration of 150 mg/mL;
 - (b) trehalose at a concentration of 240 mM;
 - (c) poloxamer 188 at a concentration of 0.5% (w/v); and
 - (d) histidine buffer at a concentration of 10 mM and having a pH of 5.5.
35. The liquid pharmaceutical formulation of any one of claims 1-34, wherein the formulation has an antibody monomer content that is at least 95.8% after 6 months of storage at 4-8°C.
36. The liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation does not exhibit visible proteinaceous particles.
37. The liquid pharmaceutical formulation of any one of claims 1-36, wherein the formulation has an opalescence after 3 months of storage at 25°C that is no more than 6 nephelometric turbidity units (NTU).
38. The liquid pharmaceutical formulation of any one of claims 1-37, wherein the formulation has an opalescence after 6 months of storage at 25°C that is no more than 6 NTU.
39. The liquid pharmaceutical formulation of any one of claims 1-38, wherein the formulation does not exhibit a change in color after six months of storage at 25°C.
40. The liquid pharmaceutical formulation of any one of claims 1-39, wherein the formulation does not affect binding of the anti-CD38 antibody to CD38.
41. The liquid pharmaceutical formulation of any one of claims 1-40, for use in the treatment of a disease or disorder.

42. The liquid pharmaceutical formulation of claim 41, wherein the disease or disorder is an inflammatory disease or disorder.

43. The liquid pharmaceutical formulation of claim 42, wherein the inflammatory disease or disorder is an autoimmune disease or disorder.

44. The liquid pharmaceutical formulation of any one of claims 1-43, formulated for subcutaneous administration.