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(54) **Title:** ANTI-INTERLEUKIN-4 RECEPTOR (IL-4R) ANTIBODY FORMULATIONS

(≥10μm) #/Container by microscopic method

5°C,	PEG 3350 Conc. (w/v)			Poloxamer 188 Conc. (w/v)		
Months	0.02%	0.04%	0.1%	0.02%	0.04%	0.1%
6	15	38	99	36	34	84
12	23	61	36	42	25	34
18	25	42	38	86	40	114
24	61	103	57	91	105	143
36	25	17	38	32	19	67

(≥25μm) #/Container by microscopic method

5°C,	PEG 3350 Conc. (w/v)			Poloxamer 188 Conc. (w/v)		
Months	0.02%	0.04%	0.1%	0.02%	0.04%	0.1%
6	0	11	42	17	2	19
12	6	19	11	17	8	4
18	8	6	11	21	4	30
24	8	13	11	11	15	15
36	15	0	6	2	4	17

FIG. 1

(57) **Abstract:** Pharmaceutical formulations comprising an antibody that specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) are provided. The formulations may contain, in addition to an anti-IL-4Rα antibody, one or more buffers, at least one amino acid, at least one sugar, and a surfactant comprising a polyethylene glycol or a poloxamer. In one aspect, the pharmaceutical formulations do not have appreciable subvisible particle formation in the presence of lipase, and exhibit a substantial degree of antibody stability during storage and after being subjected to thermal and other physical stresses.

[Continued on next page]

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ANTI-INTERLEUKIN-4 RECEPTOR (IL-4R) ANTIBODY FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Patent Application No. 63/337,532, filed May 2, 2022, the contents of which are incorporated by reference herein.

REFERENCE TO A SEQUENCE LISTING

[0002] This application incorporates by reference a computer readable Sequence Listing in ST.26 XML format, titled 11200WO01_Sequence, created on April 24, 2023 and containing 369,229 bytes.

FIELD OF THE INVENTION

[0003] The present invention relates to the field of therapeutic antibody formulations. More specifically, the present invention relates to the field of pharmaceutical formulations comprising a human antibody that specifically binds to human interleukin-4 receptor alpha.

BACKGROUND

[0004] Interleukin-4 (IL-4) and interleukin-13 (IL-13) are key cytokines in driving allergic and T helper cell type 2 (Th2) polarized inflammatory processes. IL-4 and IL-13 signaling is mediated through heterodimeric receptor complexes, in which IL-4 receptor alpha (IL-4Rα) is a shared receptor subunit for both IL-4 and IL-13 signaling. Thus, IL-4Rα is an attractive therapeutic target because it provides a single target for blocking both IL-4 and IL-13 signaling. Antibodies to hIL-4Rα are described in, for example, US Pat. Nos. 5,717,072, 7,186,809 and 7,605,237.

[0005] Therapeutic macromolecules (*e.g.*, antibodies) must be formulated in a manner that not only makes the molecules suitable for administration to patients, but also maintains their stability during storage. For example, therapeutic antibodies in liquid solution are prone to degradation, aggregation and/or undesired chemical modifications unless the solution is formulated properly. The stability of an antibody in liquid formulation depends not only on the kinds of excipients used in the formulation, but also on the amounts and proportions of the excipients relative to one another. Therapeutic formulations also may be subject to the formation of particulate matter over time during storage. Particles may be visible or subvisible; subvisible particles typically are under 150 microns or 100 microns in diameter. Formulations having high protein concentrations, e.g., concentrations of 30 mg/mL or higher, are more prone to aggregation and subvisible particle formation.

[0006] Polysorbate 20 and polysorbate 80 are commonly used in formulating biologic macromolecules such as antibodies. However, it has been reported that polysorbates, including polysorbate 20 and polysorbate 80, can degrade in the presence of lipase, which over time results in the formation of subvisible particles in a formulation. Without intending to be bound by theory, it is

believed that a putative phospholipase B-like 2 (PLBL2), which is highly conserved in hamster, rat, mice, human and bovine, copurifies with some classes of proteins under certain processes. One solution to this problem is to employ a protein purification process that removes or decreases the activity of the lipase. See, e.g., US 10,342,876. However, there remains a need for alternatives for formulating antibodies, such as anti-hIL-4Rα antibodies, in such a way that avoids or minimizes subvisible particle formation, while still maintaining sufficient stability and suitability for administration to patients.

SUMMARY

[0007] Provided herein are stable liquid pharmaceutical formulations comprising an anti-IL-4Rα antibody and one or more excipients, as well as delivery devices, kits and unit dosage forms comprising such formulations.

[0008] In one aspect, the present disclosure provides a stable liquid pharmaceutical formulation comprising: (i) a human antibody, wherein the antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα); (ii) one or more buffers; (iii) a thermal stabilizer; (iv) a viscosity reducer; and (v) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of less than 0.2% w/v, or a polyethylene glycol at a concentration of less than 1% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0009] In one aspect, the present disclosure provides a stable liquid pharmaceutical formulation comprising: (i) a human antibody, wherein the antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) and comprises a heavy chain variable region (HCVR) comprising one or more sequences disclosed in Table 1; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of less than 0.2% w/v, or a polyethylene glycol at a concentration of less than 1% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0010] In some embodiments, the antibody comprises a heavy chain variable region (HCVR) comprising complementarity determining regions HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable region (LCVR) comprising complementarity determining regions LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively. In some embodiments, the antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1, and a LCVR comprising the amino acid sequence of SEQ ID NO: 2.

[0011] In some embodiments, the antibody has a human IgG heavy chain constant region. In some cases, the heavy chain constant region is of isotype IgG1. In some cases, the heavy chain constant region is of isotype IgG4.

[0012] In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0013] In some embodiments, the surfactant is a polyethylene glycol. In some cases, the polyethylene glycol is PEG3350. In some embodiments, the surfactant is present at a concentration of from 0.0075% w/v to less than 1% w/v, from 0.0075% w/v to 0.75% w/v, from 0.01% w/v to 0.5% w/v, or from 0.01% w/v to 0.25% w/v, In some embodiments, the surfactant is present at a concentration of from 0.01% w/v to 0.19% w/v, e.g., from 0.01% w/v to 0.15% w/v or from 0.05% w/v to 0.15% w/v. In some embodiments, the surfactant is present at a concentration of no more than 0.15% w/v.

[0014] In some embodiments, the surfactant is a poloxamer. In some cases, the poloxamer is poloxamer 188. In some embodiments, the surfactant is present at a concentration of from 0.0075% w/v to 0.19% w/v, or from 0.01% w/v to 0.19% w/v, e.g., from 0.01% w/v to 0.15% w/v or from 0.05% w/v to 0.15% w/v. In some embodiments, the surfactant is present at a concentration of no more than 0.15% w/v.

[0015] In some embodiments, the buffer comprises an acetate buffer and/or a histidine buffer. In some embodiments, the buffer comprises acetate at a concentration of from 10 mM to 15 mM and/or histidine at a concentration of from 15 mM to 25 mM. In some embodiments, the acetate is present at a concentation of 12.5 mM ± 1.25 mM. In some embodiments, the histidine is present at a concentration of 20 mM ± 2 mM. In some embodiments, the thermal stabilizer is sucrose at a concentration of 5% w/v ± 0.5% w/v. In some embodiments, the viscosity reducer is arginine at a concentration of 25 mM ± 2.5 mM. In some embodiments, the arginine is present at a concentration of 50 mM ± 2.5 mM. In some embodiments, the arginine is present at a concentration of 75 mM ± 2.5 mM.

[0016] In some embodiments, the antibody is present at a concentration of up to 200 mg/mL. In some embodiments, the antibody is present at a concentration of from 15 mg/mL to 200 mg/mL. In some embodiments, the antibody is present at a concentration of from 100 mg/mL to 200 mg/mL. In some cases, the antibody is present at a concentration of 150 mg/mL ± 15 mg/mL. In some cases, the antibody is present at a concentration of 175 mg/mL ± 15 mg/mL.

[0017] In one aspect, the present disclosure provides a stable liquid pharmaceutical formulation comprising: (i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the

antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2. In some cases, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0018] In one aspect, the present disclosure provides a stable liquid pharmaceutical formulation comprising: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2. In some cases, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0019] In some embodiments, the formulation comprises a phospholipase. In some embodiments, the phospholipase protein is phospholipase B-like 2 protein.

[0020] In some embodiments, the stable liquid pharmaceutical formulation as discussed herein comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C, as determined by SE-UPLC. In some embodiments, the formulation comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C and storage at (i) 5°C for 6, 12, or 18 months, or (ii) 25°C for 6 months, as determined by SE-UPLC.

[0021] In some embodiments, the formulation comprises no more than 3% high molecular weight (HMW) species following agitation by vortexing for up to 120 minutes at room temperature, as determined by size exclusion-ultra performance liquid chromatography (SE-UPLC). In some cases, the formulation comprises no more than 2.5% high molecular weight (HMW) species following agitation by vortexing for up to 120 minutes at room temperature, as determined by SE-UPLC.

[0022] In some embodiments, the formulation comprises no more than 8% high molecular weight (HMW) species after 30 days of storage at 45ºC, as determined by SE-UPLC. In some cases, the

formulation comprises no more than 9% high molecular weight (HMW) species after 40 days of storage at 45°C, as determined by SE-UPLC. In some cases, the formulation comprises no more than 11% high molecular weight (HMW) species after 50 days of storage at 45°C, as determined by SE-UPLC.

[0023] In some embodiments, the formulation comprises no more than 1000, no more than 500, no more than 300, or no more than 150 particles having a diameter of ≥10 μm in a volume of 2.25 mL after storage for 6 months at 5°C, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

[0024] In some embodiments, the formulation comprises no more than 1000, no more than 500, no more than 300, or no more than 150 particles having a diameter of ≥10 μm in a volume of 2.25 mL after storage for 36 months at 5°C, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

[0025] In some embodiments, the formulation comprises no more than 500, no more than 300, no more than 250, or no more than 50 particles having a diameter of ≥25 μm in a volume of 2.25 mL after storage for 6 months at 5°C, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

[0026] In some embodiments, the formulation comprises no more than 500, no more than 300, no more than 250, or no more than 50 particles having a diameter of ≥25 μm in a volume of 2.25 mL after storage for 6 months at 5°C, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

[0027] In some embodiments, the formulation does not include an esterase inhibitor.

[0028] In some embodiments, the stable liquid pharmaceutical formulation is contained in a glass vial.

[0029] In some embodiments, the stable liquid pharmaceutical formulation is contained in a syringe. In some cases, the syringe comprises a fluorocarbon-coated plunger. In some cases, the syringe is a low tungsten syringe. In some cases, the syringe is a prefilled syringe. In some cases, the syringe is a prefilled staked needle syringe.

[0030] In some embodiments, the stable liquid pharmaceutical formulation is contained in a large volume device or bolus injector.

[0031] In one aspect, the present disclosure provides a pen or autoinjector delivery device containing a stable liquid pharmaceutical formulation as discussed above or herein. In some cases, the deliver device is a disposable pen delivery device. In some cases, the delivery device is a reusable pen delivery device.

[0032] In one aspect, the present disclosure provides a container containing a stable liquid pharmaceutical formulation as discussed above or herein.

[0033] In one aspect, the present disclosure provides a kit comprising (i) a container containing a stable liquid pharmaceutical formulation as discussed above or herein, and (ii) labeling for use of the pharmaceutical formulation. In some cases, the labeling recites subcutaneous administration of the pharmaceutical formulation. In some cases, the labeling recites intravenous administration of the pharmaceutical formulation.

[0034] In one aspect, the present disclosure provides a unit dosage form comprising a stable liquid pharmaceutical formulation as discussed above or herein, wherein the antibody is present in an amount of from 1 mg to 500 mg. In some cases, the antibody is present in an amount of about 100 mg. In some cases, the antibody is present in an amount of about 200 mg. In some cases, the antibody is present in an amount of about 300 mg. In some embodiments, the formulation of the unit dosage form is contained in a syringe. In some cases, the syringe is a prefilled syringe. In some embodiments, the formulation of the unit dosage form is contained in a prefilled pen. In some embodiments, the formulation of the unit dosage form is contained in an autoinjector.

[0035] In one aspect, the present disclosure provides a safety system delivery device containing a stable liquid pharmaceutical formulation as discussed above or herein. In some cases, the safety system delivery device includes a safety sleeve configured to extend by manual operation. In some cases, the safety system delivery device includes a safety sleeve configured to automatically extend following injection of the stable liquid pharmaceutical formulation.

[0036] In various embodiments, any of the features or components of embodiments discussed above or herein may be combined, and such combinations are encompassed within the scope of the present disclosure. Any specific value discussed above or herein may be combined with another related value discussed above or herein to recite a range with the values representing the upper and lower ends of the range, and such ranges are encompassed within the scope of the present disclosure. Each of the values discussed above or herein may be expressed with a variation of 1%, 5%, 10% or 20%. For example, a concentration of 10 mM may be expressed as 10 mM ± 0.1 mM (1% variation), 10 mM ± 0.5 mM (5% variation), 10 mM ± 1 mM (10% variation) or 10 mM ± 2 mM (20% variation).

[0037] Other embodiments will become apparent from a review of the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Figure 1 shows the number of particles ≥10 μm (upper panel) and ≥25 μm (lower panel) identified by microscopy in a formulation of 150 mg/mL of an anti-IL-4R antibody containing a lipase

and either PEG3350 or poloxamer 188 (at concentrations of 0.02%, 0.04%, or 0.1% w/v) and stored at 5°C for up to 36 months..

[0039] Figures 2A and 2B show the impact of PEG3350 concentrations (Fig. 2A) and poloxamer 188 concentrations (Fig. 2B) on the stability (as a percentage of high molecular weight (HMW species measured by SE-UPLC) of a formulation of 150 mg/mL of an anti-IL-4R antibody against agitation stress at room temperature for a period of from 30-120 minutes.

[0040] Figure 3 shows the impact of polysorbate 20, polysorbate 80, PEG3350, and poloxamer 188 (at varying concentrations) on the stability (as a percentage of high molecular weight (HMW species measured by SE-UPLC) of a formulation of 150 mg/mL of an anti-IL-4R antibody against thermal stress (45°C) for a period of up to 56 days.

DETAILED DESCRIPTION

[0041] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value or range of values, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0043] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, exemplary methods and materials are now described. All patents, applications and non-patent publications mentioned in this specification are incorporated herein by reference in their entireties.

Pharmaceutical Formulations

[0044] As used herein, the expression "pharmaceutical formulation" means a combination of at least one active ingredient (*e.g.*, an anti-IL-4Rα antibody, etc. which is capable of exerting a biological effect in a human or non-human animal), and at least one inactive ingredient which, when combined with the active ingredient and/or one or more additional inactive ingredients, is suitable for therapeutic administration to a human or non-human animal. The term "formulation," as used herein, means "pharmaceutical formulation" unless specifically indicated otherwise. The present

disclosure provides pharmaceutical formulations comprising at least one therapeutic polypeptide. According to certain embodiments of the present disclosure, the therapeutic polypeptide is an antibody that binds specifically to human interleukin-4 receptor alpha (hIL-4Rα) or an antigen-binding fragment thereof. More specifically, the present disclosure includes pharmaceutical formulations that comprise: (i) a human antibody that specifically binds to hIL-4Rα; (ii) one or more buffers; (iii) a thermal stabilizer; (iv) a surfactant (e.g., organic cosolvent); and (v) a viscosity modifier. Additional components may be included in the formulations of the present disclosure if such components do not significantly interfere with the viscosity and stability of the formulation. Specific exemplary components and formulations included within the present disclosure are described in detail below.

[0045] The pharmaceutical formulations of the present disclosure may, in certain embodiments, be fluid formulations. As used herein, the expression "fluid formulation" means a mixture of at least two components that exists predominantly in the fluid state at about 2ºC to about 45ºC. Fluid formulations include, *inter alia*, liquid formulations. Fluid formulations may be of low, moderate or high viscosity depending on their particular constituents.

Antibodies That Specifically Bind Human IL-4 Receptor Alpha

[0046] The pharmaceutical formulations of the present disclosure may comprise a human antibody, or an antigen-binding fragment thereof, that binds specifically to human interleukin-4 receptor alpha (IL-4Rα). References to IL-4R antibodies, herein, also refer to antibodies that bind hIL-4Rα.

[0047] The term "antibody," as used herein, is generally intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM); however, immunoglobulin molecules consisting of only heavy chains (*i.e.*, lacking light chains) are also encompassed within the definition of the term "antibody." Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementary determining regions (CDRs), 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 amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0048] In certain embodiments of the disclosure, the anti-IL-4R antibodies of the disclosure are

human antibodies. The term "human antibody," as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. In various embodiments, the anti-IL-4R antibody is a human IgG antibody. In various embodiments, the anti-IL-4R antibody is a human antibody of isotype IgG1, IgG2, IgG3 or IgG4, or mixed isotype. In some embodiments, the anti-IL-4R antibody is a human IgG1 antibody. In some embodiments, the anti-IL-4R antibody is a human IgG4 antibody. In any of the embodiments discussed above or herein, the anti-IL-4R antibody may comprise a human kappa light chain. In any of the embodiments discussed above or herein, the anti-IL-4R antibody may comprise a human lambda light chain.

[0049] The antibodies of the disclosure may, in some embodiments, be recombinant human antibodies. The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0050] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refer to one or more fragments of an antibody that retain the ability to specifically bind to hIL-4Rα.

[0051] An "isolated antibody," as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated

antibody that specifically binds hIL-4Rα is substantially free of antibodies that specifically bind antigens other than hIL-4Rα).

[0052] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by a dissociation constant of at least about $1x10^{-6}$ M or greater. Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hIL-4Rα may, however, have cross-reactivity to other antigens, such as IL-4Rα molecules from other species (orthologs). In the context of the present disclosure, multispecific (*e.g.*, bispecific) antibodies that bind to hIL-4Rα as well as one or more additional antigens are deemed to "specifically bind" hIL-4Rα. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals. However, in some instances, the isolated anibody may be copurified with a phospholipase expressed by a mammalian cell line (*e.g.*, CHO cells) from which the anti-IL-4R antibody is produced.

[0053] According to certain embodiments of the present disclosure, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises heavy chain complementarity determining regions HCDR1-HCDR2-HCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 3-4-5. According to certain embodiments of the present disclosure, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises light chain complementarity determining regions LCDR1-LCDR2-LCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 6-7-8. In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises the CDRs HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs:3-4-5-6-7-8. In some embodiments, the IL-4R antagonist is an anti-IL-4Rα antibody or antigen-binding fragment thereof that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises or consists of the amino acid sequence GFTFRDYA (SEQ ID NO:3), the HCDR2 comprises or consists of the amino acid sequence ISGSGGNT (SEQ ID NO:4), the HCDR3 comprises or consists of the amino acid sequence AKDRLSITIRPRYYGLDV (SEQ ID NO:5), the LCDR1 comprises or consists of the amino acid sequence QSLLYSIGYNY (SEQ ID NO:6), the LCDR2 comprises or consists of the amino acid sequence LGS (SEQ ID NO:7), and the LCDR3 comprises or consists of the amino acid sequence MQALQTPYT (SEQ ID NO:8).

[0054] In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises heavy chain complementarity determining regions HCDR1-HCDR2-HCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 3-4-5 and has a heavy chain

variable region (HCVR) having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO: 1. In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises light chain complementarity determining regions LCDR1-LCDR2-LCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 6-7-8 and has a light chain variable region (LCVR) having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises: heavy chain complementarity determining regions HCDR1-HCDR2-HCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 3-4-5 and has a heavy chain variable region (HCVR) having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO: 1; and light chain complementarity determining regions LCDR1-LCDR2-LCDR3, respectively, comprising the amino acid sequences of SEQ ID NOs: 6-7-8 and has a light chain variable region (LCVR) having at least 90% sequence identity (e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO: 2.

[0055] In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1. In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the anti-hIL-4R antibody, or antigen-binding fragment thereof, comprises a HCVR/LCVR amino acid sequence pair comprising the amino acid sequences of SEQ ID NOs: 1/2. In some embodiments, the anti-IL-4R antibody comprises a HCVR/LCVR comprising the amino acid sequences of SEQ ID NOs: 1/2, respectively, and a human IgG1 heavy chain constant region. In some embodiments, the anti-IL-4R antibody comprises a HCVR/LCVR comprising the amino acid sequences of SEQ ID NOs: 1/2, respectively, and a human IgG4 heavy chain constant region. In some embodiments, the anti-IL-4R antibody comprises a HCVR/LCVR comprising the amino acid sequences of SEQ ID NOs: 1/2, respectively, and a human IgG heavy chain constant region. In some embodiments, the anti-IL-4R antibody comprises a HCVR/LCVR comprising the amino acid sequences of SEQ ID NOs: 1/2, respectively, and a human IgG1 or IgG4 heavy chain constant region. In some embodiments, the anti-IL-4R antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and a light chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the anti-IL-4R antibody is dupilumab.

[0056] Other anti-IL-4R antibodies that can be used in the context of the methods of the present disclosure include, e.g., the antibody referred to and known in the art as AMG317 (Corren et al., 2010, Am J Respir Crit Care Med., 181(8):788-796), or MEDI 9314, or any of the anti-IL-4Rα antibodies as set forth in US Patent No. 7,186,809, US Patent No. 7,605,237, US Patent No. 7,638,606, US Patent No. 8,092,804, US Patent No. 8,679,487, US Patent No. 8,877,189, US Patent No. 10,774,141; US Patent Application Publication No. US2021/0238294; or International Patent Publication Nos. WO2019/228405, WO2020/096381, WO 2020/135471, WO2020/135710, or WO 2020/239134, the contents of each of which are incorporated by reference herein.

[0057] In some embodiments, the anti-IL-4R antibody comprises one or more CDR, HCVR, and/or LCVR sequences set forth in Table 1 below.

[0058] The amount of antibody, or antigen-binding fragment thereof, contained within the pharmaceutical formulations of the present disclosure may vary depending on the specific properties desired of the formulations, as well as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the pharmaceutical formulations may contain about 1 mg/mL to about 500 mg/mL of antibody; about 5 mg/mL to about 250 mg/mL of antibody; about 5 mg/mL to about 200 mg/mL of antibody; about 15 mg/mL to about 200 mg/mL; about 25 mg/mL to about 200 mg/mL of antibody; about 50 mg/mL to about 200 mg/mL of antibody; about 100 mg/mL to about 200 mg/mL; about 125 mg/mL to about 175 mg/mL; or about 150 mg/mL to about 200 mg/mL of antibody. For example, the formulations of the present disclosure may be liquid formulations that comprise about 1 mg/mL; about 2 mg/mL; about 5 mg/mL; about 10 mg/mL; about 15 mg/mL; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35 mg/mL; about 40 mg/mL; about 45 mg/mL; about 50 mg/mL; about 55 mg/mL; about 60 mg/mL; about 65 mg/mL; about 70 mg/mL; about 75 mg/mL; about 80 mg/mL; about 85 mg/mL; about 90 mg/mL; about 95 mg/mL; about 100 mg/mL; about 105 mg/mL; about 110 mg/mL; about 115 mg/mL; about 120 mg/mL; about 125 mg/mL; about 130 mg/mL; about 135 mg/mL; about 140 mg/mL; about 145 mg/mL; about 150 mg/mL; about 155 mg/mL; about 160 mg/mL; about 165 mg/mL; about 170 mg/mL; about 175 mg/mL; about 180 mg/mL; about 185 mg/mL; about 190 mg/mL; about 195 mg/mL; or about 200 mg/mL of an antibody or an antigen-binding fragment thereof, that binds specifically to hIL-4Rα. In certain embodiments, the pharmaceutical formulations are liquid formulations that may contain 5 ± 0.5 mg/mL to 200 ± 20 mg/mL of antibody; 15 ± 1.5 mg/mL to 200 ± 20 mg/mL of antibody; 25 ± 2.5 mg/mL to 200 ± 20 mg/mL of antibody; 50 ± 5 mg/mL to 200 ± 20 mg/mL of antibody; 100 ± 10 mg/mL to 200 ± 20 mg/mL of antibody; 150 ± 10 mg/mL of antibody; or 175 ± 10 mg/mL. In some embodiments, the pharmaceutical formulations contain from 140 ± 5 mg/mL to 160 ± 5 mg/mL of the anti-IL-4R antibody. In some cases, the

pharmaceutical formulations contain 165 mg/mL ± 5 mg/mL to 185 mg/mL ± 5 mg/mL of the anti-IL-4R antibody. In some cases, the pharmaceutical formulations contain 150 mg/mL ± 5 mg/mL of the anti-IL-4R antibody. In some cases, the pharmaceutical formulations contain 175 mg/mL ± 5 mg/mL of the anti-IL-4R antibody.

Bioequivalents

[0059] The present disclosure encompasses antibodies having amino acid sequences that vary from those of the exemplary molecules disclosed herein but that retain the ability to bind hIL-4R. Such variant molecules may comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the antibodies discussed herein.

[0060] The present disclosure includes antigen-binding molecules that are bioequivalent to any of the exemplary antibodies set forth herein. In some embodiments, the antigen-binding molecule is a bioequivalent of dupilumab. Two antibodies are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, *e.g.*, chronic use, and are considered medically insignificant for the particular drug product studied.

[0061] In one embodiment, two antibodies are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0062] In one embodiment, two antibodies are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0063] Bioequivalence may be demonstrated by in vivo and in vitro methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of

time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antigen-binding protein.

Formulation Excipients and pH

[0064] The pharmaceutical formulations of the present disclosure comprise one or more excipients. The term "excipient," as used herein, means any non-therapeutic agent added to the formulation to provide a desired consistency, viscosity or stabilizing effect.

[0065] The pharmaceutical formulations of the present disclosure may also comprise a buffer or buffer system, which serves to maintain a stable pH and to help stabilize the anti-IL-4R antibody. In some embodiments, the buffer or buffer system comprises at least one buffer that has a buffering range that overlaps fully or in part the range of pH 5.5 to 6.3. In various embodiments, the pH of the formulation is 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2 or 6.3. In some embodiment, the formulations have a pH of 5.9 ± 0.3. In some embodiment, the formulations have a pH of 5.9 ± 0.2. In some embodiment, the formulations have a pH of 5.9 ± 0.1. In certain embodiments, the buffer comprises a histidine buffer. In certain embodiments, the buffer comprises an acetate buffer. In certain embodiments, the buffer (*e.g.*, histidine and/or acetate) is present at a concentration of from about 1 mM to about 40 mM, about 5 mM to about 30 mM, about 10 mM to about 15 mM; or about 15 mM to about 25 mM. In some embodiments, the buffer includes a histidine buffer at a concentration of from 15 mM to 25 mM. In some embodiments, the buffer includes a histidine buffer at a concentration of 20 mM ± 2 mM. In some cases, the histidine buffer is present at a concentration of 15 mM, 16 mM, 17 mM, 18 mM, 19 mM, 20 mM, 21 mM, 22 mM, 23 mM, 24 mM, or 25 mM. In some embodiments, the buffer comprises an acetate buffer at a concentration of from 10 mM to 15 mM. In some embodiments, the buffer comprises an acetate buffer at a concentation of 12.5 mM ± 1.25 mM. In some cases, the acetate buffer is present at a concentration of 10 mM, 10.5 mM, 11 mM, 11.5 mM, 12 mM, 12.5 mM, 13 mM, 13.5 mM, 14 mM, 14.5 mM, or 15 mM. In some embodiments, the formulations of the present disclosure include both histidine and acetate buffers at any of the concentrations discussed above. In some cases, the formulations contain a histidine buffer at a concentration of from 15 mM to 25 mM, and an acetate buffer at a concentration of from 10 mM to 15 mM. In some cases, the formulations contain a histidine buffer at a concentration of 20 mM ± 2 mM, and an acetate buffer at a concentration of 12.5 mM ± 1.25 mM.

[0066] The pharmaceutical formulations of the present disclosure may also comprise one or more carbohydrates, *e.g.*, one or more sugars. The sugar can be a reducing sugar or a non-reducing sugar. "Reducing sugars" include, *e.g.*, sugars with a ketone or aldehyde group and contain a reactive hemiacetal group, which allows the sugar to act as a reducing agent. Specific examples of reducing sugars include fructose, glucose, glyceraldehyde, lactose, arabinose, mannose, xylose,

ribose, rhamnose, galactose and maltose. Non-reducing sugars can comprise an anomeric carbon that is an acetal and is not substantially reactive with amino acids or polypeptides to initiate a Maillard reaction. Specific examples of non-reducing sugars include sucrose, trehalose, sorbose, sucralose, melezitose and raffinose. Sugar acids include, for example, saccharic acids, gluconate and other polyhydroxy sugars and salts thereof. In some embodiments, the sugar is sucrose. In some cases, the sugar (*e.g.*, sucrose) acts as a thermal stabilizer for the anti-IL-4R antibody.

[0067] The amount of sugar (*e.g.*, sucrose) contained within the pharmaceutical formulations of the present disclosure will vary depending on the specific circumstances and intended purposes for which the formulations are used. In certain embodiments, the formulations may contain about 0.1% to about 20% sugar; about 0.5% to about 20% sugar; about 1% to about 20% sugar; about 2% to about 15% sugar; about 3% to about 8% sugar; or about 4% to about 6% sugar. For example, the pharmaceutical formulations of the present disclosure may comprise about 0.5%; about 1.0%; about 1.5%; about 2.0%; about 2.5%; about 3.0%; about 3.5%; about 4.0%; about 4.5%; about 5.0%; about 5.5%; about 6.0%; about 6.5%; about 7.0%; about 7.5%; about 8.0%; about 8.5%; about 9.0%; about 9.5%; about 10.0%; about 15%; or about 20% sugar (*e.g.*, sucrose). In some embodiments, the formulations contain about 5% sugar (*e.g.*, sucrose). In some embodiments, the formulations contain about 5% ± 0.5% sugar (*e.g.*, sucrose). Each of the percentages noted above corresponds to a percent weight/volume (w/v).

[0068] The pharmaceutical formulations of the present disclosure may also comprise one or more organic cosolvents in a type and in an amount that stabilizes the anti-IL-4R antibody under conditions of rough handling or agitation, such as, *e.g.,* orbital shaking. In some embodiments, the organic cosolvent is a surfactant. As used herein, the term "surfactant" means a substance which reduces the surface tension of a fluid in which it is dissolved and/or reduces the interfacial tension between oil and water. Surfactants can be ionic or non-ionic. Specific non-ionic surfactants that can be included in the formulations of the present disclosure include, *e.g.*, poloxamers such as poloxamer 188 and polyethylene glycols (PEGs) such as PEG3350.

[0069] The amount of surfactant contained within the pharmaceutical formulations of the present disclosure may vary depending on the specific properties desired of the formulations, as well as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the formulations may contain at least about 0.0075% surfactant. In certain embodiments, the formulations may contain at least about 0.01% surfactant. In certain embodiments, the formulations may contain about 0.0075% to about 0.5% surfactant. In certain embodiments, the formulations may contain less than 0.2% surfactant. In certain embodiments, the formulations may contain about 0.0075% to about 0.19% surfactant; about 0.01% to about 0.19%

surfactant; about 0.0075% to about 0.15% surfactant; about 0.01% to about 0.15% surfactant; about 0.0075% to about 0.12% surfactant; about 0.01% to about 0.12% surfactant; about 0.0075% to about 0.11% surfactant; about 0.01% to about 0.11% surfactant; about 0.0075% to about 0.1% surfactant; about 0.01% to about 0.1% surfactant; about 0.0075% to about 0.09% surfactant; or about 0.01% to about 0.09% surfactant. For example, the formulations of the present disclosure may comprise about 0.0075%; about 0.01%; about 0.02%; about 0.03%; about 0.04%; about 0.05%; about 0.06%; about 0.07%; about 0.08%; about 0.09%; about 0.1%; about 0.11%; about 0.12%; about 0.13%; about 0.14%; about 0.15%; about 0.16%; about 0.17%; about 0.18%; or about 0.19% surfactant (*e.g.*, poloxamer 188 or PEG3350). In some embodiments, the formulations contain less than 0.2% poloxamer (e.g., poloxamer 188). In some embodiments, the formulations contain about 0.0075% to 0.19% poloxamer 188. In some embodiments, the formulations contain about 0.01% to 0.19% poloxamer 188. In some embodiments, the formulations contain less than 1% polyethylene glycol (e.g., PEG3350). In some embodiments, the formulations contain about 0.0075% to about 0.5% PEG3350. In some embodiments, the formulations contain about 0.01% to 0.19% PEG3350. Each of the percentages noted above corresponds to a percent weight/volume (w/v).

[0070] In certain embodiments, the pharmaceutical formulations of the disclosure comprise at least one amino acid. In some embodiments, the amino acid is arginine. In some embodiments, the arginine is provided in the form of arginine hydrochloride. In some cases, the amino acid (*e.g.*, arginine) acts as a viscosity modifier for the anti-IL-4R antibody formulations.

[0071] The amount of amino acid contained within the pharmaceutical formulations of the present disclosure may vary depending on the specific properties desired of the formulations, as well as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the formulations may contain about 1 mM to about 200 mM of an amino acid; about 5 mM to about 150 mM; about 10 mM to about 100 mM of an amino acid; about 20 mM to about 80 mM of an amino acid; about 20 mM to about 30 mM of an amino acid; about 45 mM to about 55 mM of an amino acid; or about 70 mM to about 80 mM of an amino acid. For example, the pharmaceutical formulations of the present disclosure may comprise about 5 mM; about 10 mM; about 15 mM; about 20 mM; about 25 mM; about 30 mM; about 35 mM; about 40 mM; about 45 mM; about 50 mM; about 55 mM; about 60 mM; about 65 mM; about 70 mM; about 75 mM; about 80 mM; about 85 mM; about 90 mM; about 95 mM; or about 100 mM of an amino acid (*e.g.*, arginine). In some embodiments, the formulations contain about 25 mM of an amino acid (*e.g.*, arginine). In some embodiments, the formulations contain about 50 mM of an amino acid (*e.g.*,

arginine). In some embodiments, the formulations contain about 75 mM of an amino acid (*e.g.*, arginine).

Exemplary Formulations

[0072] According to one aspect of the present disclosure, the pharmaceutical formulation comprises: (i) a human antibody that specifically binds to hIL-4R (*e.g.*, an antibody comprising one or more sequences disclosed in Table 1 below); (ii) acetate; (iii) histidine; (iv) sucrose; (v) arginine; and (v) a surfactant comprising a polyethylene glycol or a poloxamer.

[0073] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody that specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0074] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody that specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol at a concentration of from 0.01% w/v to less than 1% w/v (e.g., from 0.01% to 0.75% w/v, or from 0.01% to 0.5% w/v), wherein the formulation has a pH of from 5.7 to 6.1.

[0075] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 15 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0076] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 15 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0077] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 15 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0078] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 15 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0079] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 100 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a

polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0080] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 100 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0081] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 100 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0082] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of from 100 mg/mL to 200 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0083] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at

a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0084] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0085] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0086] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0087] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid

sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0088] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentration of from 10 mM to 15 mM; (iii) histidine at a concentration of from 15 mM to 25 mM; (iv) sucrose at a concentration of from 2.5% w/v to 7.5% w/v; (v) arginine at a concentration of from 20 mM to 80 mM; and (vi) PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of from 5.7 to 6.1.

[0089] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0090] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 25 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0091] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 50 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0092] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 50 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0093] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 75 mM ± 2.5 mM; and (vi) a surfactant comprising PEG3350 at a concentration of from 0.01% w/v to 0.19% w/v or at a concentration of from 0.01% w/v to 0.5% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0094] In some cases, the stable liquid pharmaceutical formulation comprises: (i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human IL-4Rα and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2; (ii) acetate at a concentation of 12.5 mM ± 1.25 mM; (iii) histidine at a concentration of 20 mM ± 2 mM; (iv) sucrose at a concentration of 5% w/v ± 0.5% w/v; (v) arginine at a concentration of 75 mM ± 2.5 mM; and (vi) a surfactant comprising poloxamer 188 at a

concentration of from 0.01% w/v to 0.19% w/v, wherein the formulation has a pH of 5.9 ± 0.3 or a pH of 5.9 ± 0.2.

[0095] In any of the various embodiments of the pharmaceutical formulations discussed above or herein, the human IL-4R antibody may comprise a human IgG1 heavy chain constant region.

[0096] In any of the various embodiments of the pharmaceutical formulations discussed above or herein, the human IL-4R antibody may comprise a human IgG4 heavy chain constant region.

[0097] In some embodiments, the human IL-4R antibody may comprise a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

[0098] Additional non-limiting examples of pharmaceutical formulations encompassed by the present disclosure are set forth elsewhere herein, including the working Examples presented below.

Stability of the Pharmaceutical Formulations

[0099] The pharmaceutical formulations of the present disclosure exhibit high levels of stability. The term "stable," as used herein in reference to the pharmaceutical formulations, means that the antibodies within the pharmaceutical formulations retain an acceptable degree of structure and/or function and/or biological activity after storage for a defined amount of time. A formulation may be stable even though the antibody contained therein does not maintain 100% of its structure and/or function and/or biological activity after storage for a defined amount of time. Under certain circumstances, maintenance of about 90%, about 95%, about 96%, about 97%, about 98% or about 99% of an antibody's structure and/or function and/or biological activity after storage for a defined amount of time may be regarded as "stable."

[0100] Stability can be measured, *inter alia*, by determining the percentage of antibody that forms an aggregate within the formulation after storage for a defined amount of time at a defined temperature, or under stress conditions (*e.g.*, agitation), wherein stability is inversely proportional to the percent aggregate that is formed. The percentage of aggregated antibody can be determined by, *inter alia*, size exclusion chromatography (*e.g.*, size exclusion high performance liquid chromatography [SE-HPLC] or size exclusion ultra-performance liquid chromatography [SE-UPLC]). An "acceptable degree of stability", as that phrase is used herein, means that at most about 15%, 10%, 5%, 4%, 3%, 2.5%, 2%, 1.5%, 1%, 0.5%, or 0.1% of the antibody can be detected in an aggregate in the formulation after storage for a defined amount of time at a given temperature, or under specified stress conditions. The defined amount of time after which stability is measured can be at least 2 weeks, at least 28 days, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24

months, at least 30 months, at least 36 months, or more. The temperature at which the pharmaceutical formulation may be stored when assessing stability can be any temperature from about -80ºC to about 45ºC, *e.g.*, storage at about -80ºC, about -30ºC, about -20ºC, about 0ºC, about 4º-8°C, about 5ºC, about 25ºC, about 35ºC, about 37ºC or about 45ºC. The "stress condition" to which the formulated antibody may be subjected may be agitation stress (*e.g.*, vortexing) for a period of 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutues, 70 minutes, 80 minutes, 90 minutes, 100 minutes, 110 minutes, 120 minutes, 150 minutes, 180 minutres, or more. For example, a pharmaceutical formulation comprising an anti-IL-4R antibody may be deemed stable if after nine months of storage at 5ºC, less than about 2%, 1.75%, 1.5%, 1.25%, 1%, 0.75%, 0.5%, 0.25%, or 0.1% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after 56 days of storage at 45ºC, less than about 12% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after 42 days of storage at 45ºC, less than about 10% or less than about 9% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after 28 days of storage at 45ºC, less than about 8% or less than about 7.5% or less than about 7% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after 14 days of storage at 45ºC, less than about 6% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after three months of storage at -20ºC, -30ºC, or -80ºC less than about 2%, 1.9%, 1.8%, 1.7%, 1.6%, 1.5%, 1%, 0.5%, or 0.1% of the antibody is detected in an aggregated form. A pharmaceutical formulation may also be deemed stable if after 120 minutes of agitation (*e.g.*, via vortexing) at room temperature less than 3% or less than 2.5% of the antibody is detected in an aggregated form. In some cases, a pharmaceitical formulation may be deemed stable if it comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C, as determined by SE-UPLC. In some cases, the formulation may be deemed stable if it comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C and storage at (i) 5°C for 6, 12, or 18 months, or (ii) 25°C for 6 months, as determined by SE-UPLC.

[0101] Stability can also be measured, *inter alia*, by determining particulate formulation within the formulation after storage for a defined amount of time at a defined temperature. Particle formation can be determined, for example, by microscopy techniques or by micro-flow imaging techniques.

[0102] It is known that mammalian cell lines routinely used to produce recombinant antibodies may contain enzymes that may be copurified with the antibody and be present in a pharmaceutical formulation of the antibody. In some cases, such enzymes may degrade excipients of the pharmaceutical formulation over time, and thereby lead to formation of subvisible particles (*e.g.*, on

the order of 10-25 μm or larger). For example, phospholipases are lipases that hydrolyze phospholipids into fatty acids and other products. Phospholipases fall into four broad categories: phospholipase A (including phospholipase A1 and phospholipase A2), phospholipase B, and the phosphodiesterases phosphodiesterase C and phosphodiesterase D. In addition to the canonical phospholipases, phospholipase B-like enzymes, which reside at the lysosome lumen, are thought to be involved in lipid catalysis. For example, phospholipase B-like 2 (PLBL2) is postulated to have esterase activity based upon sequence homology and subcellular localization (Jensen *et al.*, Biochem. J. 402: 449-458 (2007)). PLBL2 is highly conserved in hamster, rat, mice, human and bovine, and may copurify under certain processes with some classes of proteins-of-interest (*e.g.*, a therapeutic antibody such as an anti-IL-4R antibody) manufactured in a mammalian cell line. Although it is possible to remove such enzymes via purification or to include an inhibitor (*e.g.*, an esterase inhibitor) to counteract the activity of the enzyme (as disclosed for example in US Patent No. 10,342,876), selection of excipients that prevent particle formation while also stabilizing the antibody in the pharmaceutical formulation are also of interest. Thus, in some embodiments, the formulations of the present disclosure comprise a detectable amount of a phospholipase (e.g., PLBL2). Methods of detecting and quantifying the presence and activity of phospholipase are known in the art. In some embodiments, the phospholipase is detected by immunoassay (e.g., ELISA). In some embodiments, the phospholipase is detected by liquid chromatography-mass spectrometry (LC-MS)

[0103] Accordingly, a pharmaceutical formulation (containing a phospholipase) may be deemed stable if after storage for a period of time (*e.g.*, 6, 12, 18, 24 or 36 months or more) at a defined temperature (*e.g.*, 5°C), no more than a specified number of particles (*e.g.*, 3000 particles, 1000 particles, 500 particles, 250 particles, 100 particles, or 50 particles per container for ≥ 10 micron) are identified within a volume of 2.25 mL. For example, a pharmaceutical formulation may be deemed stable if after 24 months of storage at 5°C no more than 1000 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 24 months of storage at 5°C no more than 500 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 24 months of storage at 5°C no more than 250 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 24 months of storage at 5°C no more than 150 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 1000 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 500 particles are

identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 250 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 150 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 100 particles are identified within a volume of 2.25 mL via microscopy. A pharmaceutical formulation may also be deemed stable if after 36 months of storage at 5°C no more than 50 particles are identified within a volume of 2.25 mL via microscopy.

[0104] Stability can also be measured by, *inter alia*, determining the percentage of native antibody remaining in the formulation after storage for a defined amount of time at a given temperature. The percentage of native antibody can be determined by, *inter alia*, size exclusion chromatography (*e.g.*, size exclusion high performance liquid chromatography [SE-HPLC]). An "acceptable degree of stability," as that phrase is used herein, means that at least 90% of the native form of the antibody can be detected in the formulation after storage for a defined amount of time at a given temperature. In certain embodiments, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of the native form of the antibody can be detected in the formulation after storage for a defined amount of time at a given temperature. The defined amount of time after which stability is measured can be at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months, or more. The temperature at which the pharmaceutical formulation may be stored when assessing stability can be any temperature from about -80ºC to about 45ºC, *e.g.*, storage at about -80ºC, about -30ºC, about -20ºC, about 0ºC, about 2°-8°C, 4º-8°C, about 5ºC, about 25ºC, about 35ºC, about 37ºC, or about 45ºC.

[0105] Stability can also be measured, *inter alia*, by determining the percentage of antibody that migrates in a more acidic fraction during ion exchange ("acidic form") than in the main fraction of antibody ("main charge form"), wherein stability is inversely proportional to the fraction of antibody in the acidic form. While not wishing to be bound by theory, deamidation of the antibody may cause the antibody to become more negatively charged and thus more acidic relative to the non-deamidated antibody (see, *e.g.,* Robinson, N., Protein Deamidation, *PNAS*, April 16, 2002, 99(8):5283-5288). The percentage of "acidified" antibody can be determined by ion exchange chromatography (*e.g.*, cation exchange high performance liquid chromatography [CEX-HPLC] or cation exchange ultra-performance liquid chromatography [CEX-UPLC]). An "acceptable degree of stability", as that phrase is used herein, means that at most 50%, 45%, 40%, 35%, 30%, 25%, 20%,

15%, 10%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.1% of the antibody can be detected in an acidic form in the formulation after storage for a defined amount of time at a given temperature. The defined amount of time after which stability is measured can be at least 2 weeks, at least 28 days, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months, or more. The temperature at which the pharmaceutical formulation may be stored when assessing stability can be any temperature from about -80ºC to about 45ºC, *e.g.*, storage at about -80ºC, about -30ºC, about -20ºC, about 0ºC, about 4º-8ºC, about 5ºC, about 25ºC, or about 45ºC.

[0106] Measuring the binding affinity of the antibody to its target may also be used to assess stability. For example, a formulation of the present disclosure may be regarded as stable if, after storage at *e.g.*, -80ºC, -30ºC, -20ºC, 5ºC, 25ºC, 37ºC, 45ºC, etc. for a defined amount of time (*e.g.*, 14 days to 9 months), the anti-IL-4R antibody contained within the formulation binds to hIL-4Rα with an affinity that is at least 80%, 85%, 90%, 95%, or more of the binding affinity of the antibody prior to said storage. Binding affinity may be determined by any method, such as *e.g.,* ELISA or plasmon resonance. Biological activity may be determined by, for example, measuring the downstream activity of the IL-4R system in the presence of the antibody, and comparing the activity to the activity of the IL-4R system in the absence of antibody.

[0107] References to stability of the pharmaceutical formulations "after" a specified period of time are intended to mean that a measurement of a stability parameter (*e.g.,* % native form, % HMW species, or % acidic form) is taken at or about the end of the specific time period, and is not intended to mean that the pharmaceutical formulation necessarily maintains the same degree of stability for the measured parameter thereafter. For example, reference to a particular stability after 12 months means that the measurement of stability was taken at or about 12 months after the start of the study. Additional methods for assessing the stability of an antibody in formulation are demonstrated in the Examples presented below.

[0108] As illustrated in the Examples below, the present disclosure is based, in part, on the discovery that the combination of claimed excipients with an anti-IL-4R antibody produces a formulation that is stable over long periods (*e.g.*, 36 months) of storage.

Containers and Methods of Administration

[0109] The pharmaceutical formulations of the present disclosure may be contained within any container suitable for storage of medicines and other therapeutic compositions. For example, the pharmaceutical formulations may be contained within a sealed and sterilized plastic or glass container having a defined volume such as a vial, ampule, syringe, cartridge, bottle or IV bag.

Different types of vials can be used to contain the formulations of the present disclosure including, *e.g.,* clear and opaque (*e.g.*, amber) glass or plastic vials. Likewise, any type of syringe can be used to contain and/or administer the pharmaceutical formulations of the present disclosure. In some embodiments, the pharmaceutical formulation is contained in a prefilled syringe. In some embodiments, the pharmaceutical formulation is contained in a prefilled staked needle syringe.

[0110] The pharmaceutical formulations of the present disclosure may be contained within "normal tungsten" syringes or "low tungsten" syringes. As will be appreciated by persons of ordinary skill in the art, the process of making glass syringes generally involves the use of a hot tungsten rod which functions to pierce the glass thereby creating a hole from which liquids can be drawn and expelled from the syringe. This process results in the deposition of trace amounts of tungsten on the interior surface of the syringe. Subsequent washing and other processing steps can be used to reduce the amount of tungsten in the syringe. As used herein, the term "normal tungsten" means that the syringe contains greater than 500 parts per billion (ppb) of tungsten. The term "low tungsten" means that the syringe contains less than 500 ppb of tungsten. For example, a low tungsten syringe, according to the present disclosure, can contain less than about 490, 480, 470, 460, 450, 440, 430, 420, 410, 390, 350, 300, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 or fewer ppb of tungsten.

[0111] The rubber plungers used in syringes, and the rubber stoppers used to close the openings of vials, may be coated to prevent contamination of the medicinal contents of the syringe or vial and/or to preserve their stability. Thus, pharmaceutical formulations of the present disclosure, according to certain embodiments, may be contained within a syringe that comprises a coated plunger, or within a vial that is sealed with a coated rubber stopper. For example, the plunger or stopper may be coated with a fluorocarbon film. Examples of coated stoppers and/or plungers suitable for use with vials and syringes containing the pharmaceutical formulations of the present disclosure are mentioned in, *e.g.*, U.S. Patent Nos. 4,997,423; 5,908,686; 6,286,699; 6,645,635; and 7,226,554, the contents of which are incorporated by reference herein in their entireties. Particular exemplary coated rubber stoppers and plungers that can be used in the context of the present disclosure are commercially available under the tradename "FluroTec®," available from West Pharmaceutical Services, Inc. (Lionville, PA). According to certain embodiments of the present disclosure, the pharmaceutical formulations may be contained within a low tungsten syringe that comprises a fluorocarbon-coated plunger. In some embodiments, the container is a syringe, such as an Ompi EZ-Fill™ syringe or a BD Neopak™ syringe. In some cases, the syringe is a 1 mL long glass syringe with a 1 mL iWest piston, a 27G thin wall needle and an FM30 needle shield or a BD260 needle shield. In some cases, the syringe is a 2.25 mL glass syringe (*e.g.*, Nuova Ompi).

In various embodiments, the syringe is a 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, 0.9 mL, 1.0 mL, 1.1 mL, 1.2 mL, 1.3 mL, 1.4 mL, 1.5 mL, 1.6 mL, 1.7 mL, 1.8 mL, 1.9 mL, 2.0 mL, 2.1 mL, 2.2 mL, 2.3 mL, 2.4 mL, 2.5 mL, 2.6 mL, 2.7 mL, 2.8 mL, 2.9 mL, 3.0 mL, 3.5 mL, 4.0 mL, 4.5 mL, 5.0 mL, 5.5 mL, 6.0 mL, 6.5 mL, 7.0 mL, 7.5 mL, 8.0 mL, 8.5 mL, 9.0 mL, 9.5 mL, or 10 mL syringe (*e.g.*, a glass syringe).

[0112] The pharmaceutical formulations can be administered to a patient by parenteral routes such as injection (*e.g.*, subcutaneous, intravenous, intramuscular, intraperitoneal, etc.) or percutaneous, mucosal, nasal, pulmonary and/or oral administration. Numerous reusable pen and/or autoinjector delivery devices can be used to subcutaneously deliver the pharmaceutical formulations of the present disclosure. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen and/or autoinjector delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present disclosure include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park, IL), to name only a few. In some cases, the pharmaceutical formulation is contained in a syringe specifically adapted for use with an autoinjector. Subcutaneous injections may be administered using a 20-30 gauge needle, or a 25-30 gauge needle. In some cases, subcutaneous injections may be administered using a 25 gaude needle. In some cases, subcutaneous injections may be administered using a 27 gaude needle. In some cases, subcutaneous injections may be administered using a 29 gaude needle.

[0113] Another type of delivery device can include a safety system. Such devices can be relatively inexpensive, and operate to manually or automatically extend a safety sleeve over a needle once injection is complete. Examples of safety systems can include the ERIS device by West Pharmaceutical, or the UltraSafe device by Becton Dickinson. In addition, the use of a large volume device ("LVD"), or bolus injector, to deliver the pharmaceutical formulations of the present disclosure is also contemplated herein. In some cases, the LVD or bolus injector may be

configured to inject a medicament into a patient. For example, an LVD or bolus injector may be configured to deliver a "large" volume of medicament (typically about 2 mL to about 10 mL).

[0114] In some embodiments, a pharmaceutical composition comprising an anti-IL-4R antibody is administered using a drug delivery device that is a needle-based injection system as described in Table 1 of section 5.2 of ISO 11608-1:2014(E). As described in ISO 11608-1:2014(E), needle-based injection systems may be broadly distinguished into multi-dose container systems and single-dose (with partial or full evacuation) container systems. The container may be a replaceable container or an integrated non-replaceable container.

[0115] As further described in ISO 11608-1:2014(E), a multi-dose container system may involve a needle-based injection device with a replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user). Another multi-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).

[0116] As further described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with a replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation). As also described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation).

[0117] An exemplary sleeve-triggered auto-injector with manual needle insertion is described in International Publication WO2015/004052. Exemplary audible end-of-dose feedback mechanisms are described in International Publications WO2016/193346 and WO2016/193348. An exemplary needle-safety mechanism after using an auto-injector is described in International Publication WO2016/193352. An exemplary needle sheath remover mechanism for a syringe auto-injector is described in International Publication WO2016/193353. An exemplary support mechanism for supporting an axial position of a syringe is described in International Publication WO2016/193355.

[0118] The pharmaceutical formulations of the present disclosure can also be contained in a unit dosage form. The term "unit dosage form," as used herein, refers to a physically discrete unit suitable as a unitary dosage for the patient to be treated, each unit containing a predetermined

quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier, diluent, or excipient. In various embodiments, the unit dosage form is contained within a container as discussed herein. Actual dosage levels of the active ingredient (*e.g.*, an anti-IL-4R antibody) in the formulations of the present disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without adverse effect to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present disclosure employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts. The term "diluent" as used herein refers to a solution suitable for altering or achieving an exemplary or appropriate concentration or concentrations as described herein.

[0119] In various embodiments, the unit dosage form contains an amount of the active ingredient (*e.g.*, an anti-IL-4R antibody) intended for a single use. In various embodiments, the amount of the active ingredient in the unit dosage form is from about 0.1 mg to about 5000 mg, from about 100 mg to about 1000 mg, and from about 100 mg to about 500 mg, from about 100 mg to about 400 mg, from about 100 mg to about 200 mg, from about 250 mg to about 350 mg, from about 125 mg to about 175 mg, from about 275 mg to about 325 mg, or ranges or intervals thereof. For example, ranges of values using a combination of any of the above recited values (or values contained within the above recited ranges) as upper and/or lower limits are intended to be included. In a particular embodiment, the formulation often is supplied as a liquid in unit dosage form. In some embodiments, the unit dosage form contains about 100 mg of the active ingredient. In some embodiments, the unit dosage form contains about 150 mg. In some embodiments, the unit dosage form contains about 200 mg. In some embodiments, the unit dosage form contains about 300 mg. In some embodiments, the unit dosage form contains about 350 mg. In some embodiments, the unit dosage form contains about 600 mg. In some embodiments, a unit dosage form according to the present disclosure is suitable for subcutaneous administration to a patient.

[0120] The present disclosure also includes methods of preparing a unit dosage form. In an exemplary embodiment, a method for preparing a pharmaceutical unit dosage form includes combining the formulation of any of foregoing embodiments in a suitable container (*e.g.*, those containers discussed herein).

Therapeutic Uses of the Pharmaceutical Formulations

[0121] The pharmaceutical formulations of the present disclosure are useful, *inter alia*, for the treatment, prevention and/or amelioration of any disease or disorder associated with IL-4R activity.

[0122] The therapeutic methods of the present disclosure comprise administering to a subject any formulation comprising an anti-hIL-4R antibody as disclosed herein. The subject to which the pharmaceutical formulation is administered can be, *e.g.*, any human or non-human animal that is in need of such treatment, prevention and/or amelioration, or who would otherwise benefit from the inhibition or attenuation of IL-4R and/or IL-4R-mediated activity. The present disclosure further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of any disease or disorder associated with IL-4R activity.

[0123] In some embodiments, the disease or disorder associated with IL-4R activity is an inflammatory condition, allergic condition, lung/respiratory disorder, gastrointestinal disorder, or dermatological disorder. In some embodiments, the disease or disorder is a Type 2 inflammatory disorder. In some embodiments, the disease or disorder is an atopic disease. Non-limiting examples of diseases and disorders associated with IL-4R activity include allergy (e.g., food allergy or environmental allergy), allergic reactions, allergic bronchopulmonary aspergillosis, alopecia areata, asthma (including mild, moderate, or severe asthma, persistent asthma, or allergic asthma), arthritis (including septic arthritis), atopic dermatitis (including moderate or severe atopic dermatitis), atopic keratoconjunctivitis, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome, autoimmune uveitis, Barrett's esophagus, benign prostate hyperplasia, bronchiectasis, bullous pemphigoid, Churg-Strauss syndrome, chronic idiopathic urticaria, chronic inducible urticaria, cold inducible urticaria, contact dermatitis (e.g., allergic contact dermatitis), COPD, eosinophilic esophagitis, eosinophilic duodenitis, eosinophilic gastroenteritis, Grave's disease, herpetiformis, hypertrophic scarring, inflammatory bowel disease, Kawasaki disease, nasal polyposis, nephrosis, Netherton's syndrome, pre-eclampsia, prurigo nodularis, pruritus (e.g., chronic pruritus of unknown origin), rhinitis (e.g., allergic rhinitis), rhinosinusitis (e.g., allergic fungal rhinosinusitis, chronic rhinosinusitis with or without nasal polyposis), scleroderma, sickle cell disease, Sjogren's syndrome, tuberculosis, ulcerative colitis, and Whipple's Disease.

[0124] In some embodiments, the present disclosure provides kits comprising a pharmaceutical formulation (*e.g.*, a container with the formulation or a unit dosage form), as discussed herein, and packaging or labeling (*e.g.*, a package insert) with instructions to use the pharmaceutical formulation for the treatment of a disease or disorder, as discussed above. In some cases, the instructions provide for use of a unit dosage form, as discussed herein, for the treatment of a

disease or disorder.

[0125] A summary of the sequences and the corresponding SEQ ID NOs referenced herein is shown in Table 1, below.

Table 1: Informal Sequence Listing

SEQ ID NO	Sequence	Description
1	EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSISGSG GNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPRYYGLD VWGQGTTVTVS	Dupilumab HCVR amino acid sequence
2	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIYLGSNR ASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEIK	Dupilumab LCVR amino acid sequence
3	GFTFRDYA	Dupilumab HCDR1 amino acid sequence
4	ISGSGGNT	Dupilumab HCDR2 amino acid sequence
5	AKDRLSITIRPRYYGLDV	Dupilumab HCDR3 amino acid sequence
6	QSLLYSIGYNY	Dupilumab LCDR1 amino acid sequence
7	LGS	Dupilumab LCDR2 amino acid sequence
8	MQALQTPYT	Dupilumab LCDR3 amino acid sequence
9	EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSISGSG GNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPRYYGLD VWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	Dupilumab heavy chain amino acid sequence
10	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIYLGSNR ASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Dupilumab light chain amino acid sequence
11	MKVLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENNGGA GCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPRAPGNLTVHTNVS DTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLKSGI SYRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQH	Human IL-4Rα
12	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-39
13	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-40
14	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-41
15	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-42
16	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-43

17	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-44
18	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-45
19	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSAGWTFGQGTKVEIK	SCB-VL-46
20	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-47
21	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-48
22	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-49
23	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-50
24	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-51
25	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-52
26	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-53
27	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-54
28	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-55
29	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-56
30	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-57
31	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-58
32	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-59
33	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-60
34	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-61
35	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-62
36	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-63
37	EVQLVESGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-64
38	EVQLVESGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-65

39	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-66
40	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-67
41	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-68
42	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-69
43	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQG TLVTVSS	SCB-VH-70
44	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-71
45	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-72
46	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-73
47	EVQLVQSGGGLVHPGRSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-74
48	EVQLVQSGGGLVHPGGSLRLTCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-75
49	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMHWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-76
50	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGEGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-77
51	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDEAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-78
52	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAGDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-79
53	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFDDYAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-80
54	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-81
55	EVQLVESGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-82

56	EVQLVESGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-83
57	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-84
58	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-85
59	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-86
60	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-87
61	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-88
62	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-89
63	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-90
64	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-91
65	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-92
66	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-93
67	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLDYWGKG TLVTVSS	MEDI-1-VH
68	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSLSANYVFGTGTKLTVL	MEDI-1-VL
69	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-2-VH
70	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSQPPNPLFGTGTKLTVL	MEDI-2-VL
71	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKLLKNPWGKGT LVTVSS	MEDI-3-VH
72	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWFGTPASNYVFGTGTKLTVL	MEDI-3-VL
73	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-4-VH

74	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-4-VL
75	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-5-VH
76	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-5-VL
77	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-6-VH
78	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-6-VL
79	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQYWGK GTLVTVSS	MEDI-7-VH
80	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-7-VL
81	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQYWGK GTLVTVSS	MEDI-8-VH
82	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-8-VL
83	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-9-VH
84	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTMYPLFGTGTKLTVL	MEDI-9-VL
85	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-10-VH
86	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVLTPIFGTGTKLTVL	MEDI-10-VL
87	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWFYDWGKG TLVTVSS	MEDI-11-VH
88	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPSMIPLFGTGTKLTVL	MEDI-11-VL
89	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWFYDWGKG TLVTVSS	MEDI-12-VH
90	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTMYPLFGTGTKLTVL	MEDI-12-VL
91	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-13-VH
92	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTLQPLFGTGTKLTVL	MEDI-13-VL
93	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-14-VH
94	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPPTKPLFGTGTKLTVL	MEDI-14-VL

95	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-15-VH
96	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTHRHPLFGTGTKLTVL	MEDI-15-VL
97	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-16-VH
98	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-16-VL
99	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-17-VH
100	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVDRPIFGTGTKLTVL	MEDI-17-VL
101	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-18-VH
102	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTPMPVFGTGTKLTVL	MEDI-18-VL
103	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-19-VH
104	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-19-VL
105	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-20-VH
106	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-20-VL
107	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-21-VH
108	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEAVYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-21-VL
109	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-22-VH
110	QPVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-22-VL
111	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-23-VH
112	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPP GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-23-VL
113	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-24-VH
114	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-24-VL

115	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSASYAQKFQGRVSMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-25-VH
116	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTTATLAITGLQTGDEADYYCGTWVTSTVWEWPFGTGTKLTVL	MEDI-25-VL
117	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-26-VH
118	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-26-VL
119	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTQVTVSS	MEDI-27-VH
120	QSVLTQPPLVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGTAPKLLIYDNNKRPSG IPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-27-VL
121	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGN GTLVTVSS	MEDI-28-VH
122	LPVLTQPPSVSAAPGQKVTISCSGGSSSIGNSYVSWYQQLPGAAPKLLIYDNNKRPSG IPDRFSGFRSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-28-VL
123	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TRVTVSS	MEDI-29-VH
124	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-29-VL
125	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-30-VH
126	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGAAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-30-VL
127	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-31-VH
128	QSVLTQPPSVSAAPGQKVTISCSGGSSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPSG IPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWATSPVWEWPFGTGTKLTVL	MEDI-31-VL
129	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-32-VH
130	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTAWEWPFGTGTKLTVL	MEDI-32-VL
131	QVQLVQSGAEEKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-33-VH
132	QSALTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-33-VL
133	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVSMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-34-VH
134	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-34-VL

135	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-35-VH
136	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-35-VL
137	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-36-VH
138	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDSSTVWEWPFGTGTKLTVL	MEDI-36-VL
139	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVAMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-37-VH
140	QSVLTQPPSVSAAPGQKVTISCSGGGSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GVPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-37-VL
141	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-38-VH
142	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-38-VL
143	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-39-VH
144	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTAWEWPFGTGTKLTVL	MEDI-39-VL
145	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-40-VH
146	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDSSTVWEWPFGTGTKLTVL	MEDI-40-VL
147	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTLVTVSG	MEDI-41-VH
148	QSVLTQPPSVSAAPGQKVTISCSGGSTNIGNSYVSWYQRLPGTAPKLLIYDNNKRPP GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-41-VL
149	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWVGIINPSG GSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSGDTAVYYCARGKYWMYDWGKGT LVTVSS	MEDI-42-VH
150	QAVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGAAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTGWEWPFGTGTKLTVL	MEDI-42-VL
151	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWVRQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-37GL-VH
152	QSVLTQPPSVSAAPGQKVTISCSGGGSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-37GL-VL
153	EVQLLESGGGLVQPGGSLRLSCAVSGFTFSNYAMSWVRQAPGKGLEWVSAISSGGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLRRYFDYWGQGTLVT VSS	AJOU-1-VH
154	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVSAISSGGS SIYYADSVKGRFTISRDNSKNTLHLQMNSLRAEDTAVYYCARGPQRSATAVFDYWG QGTLVTVSS	AJOU-2-VH

155	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSWISPNS GNIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRPLSAAWSHSSYYN AMDVWGQGTLVTVSS	AJOU-3-VH
156	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVSLISHSGS NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPHRAFDYWGQGTLV TVSS	AJOU-4-VH
157	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSGISHGS GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPHRAFDYWGQGTLV TVSS	AJOU-5-VH
158	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSGISHGN GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTGRHFDYWGQGTLV TVSS	AJOU-6-VH
159	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSSISPSGS SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSYRAFDYWGQGTLVT VSS	AJOU-7-VH
160	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISPSGG SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAKRAFDYWGQGTLVT VSS	AJOU-8-VH
161	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISPGSG STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFRRHFDYWGQGTLVT VSS	AJOU-9-VH
162	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISSGGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-10-VH
163	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGR SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLVT VSS	AJOU-69-VH
164	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGA NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-70-VH
165	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-71-VH
166	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITAGG GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-72-VH
167	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRHAMAWVRQAPGKGLEWVSAITSSGR SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLVT VSS	AJOU-83-VH
168	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVNWYQQLPGTAPKLLIYDNSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDASLSAYVFGGGTKLTVL	AJOU-33-VL
169	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNNVSWYQQLPGTAPKLLIYANSKRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDDSLSAYVFGGGTKLTVL	AJOU-34-VL
170	QSVLTQPPSAPGTPGQRVTISCTGSSSNIGSNSVNWYQQLPGTAPKLLIYDDSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCDAWDSSLSAYVFGGGTKLTVL	AJOU-35-VL
171	QSVLTQPPSASGTPGQRVTLSCTGSSSNIGSNYVSWYQQLPGTAPKLLIYADSQRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDDSLSGYVFGGGTKLTVL	AJOU-36-VL
172	QSVLTQPPSASGTPGQRVTISCSSSSSNIGSNYVSWYQQLPGTAPKLLIYSDSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-37-VL
173	QSVLTQPPSASGTPGQRVTISCTGSSSNIGNNTVSWYQQLPGTAPKLLIYDNSHRPS GVPDRFSGSKSGTSASLAISGLQSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-38-VL

174	QSVLTQPPSASGTPGQRVTISCTGSSSNIGNNDVNWYQQLPGTAPKLLIYYDSQRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCATWDASLSAYVFGGGTKLTVL	AJOU-39-VL
175	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNAVNWYQQLPGTAPKLLIYYDNQRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDDSLNGYVFGGGTKLTVL	AJOU-40-VL
176	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVTWYQQLPGTAPKLLIYDDSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-41-VL
177	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-42-VL
178	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-77-VL
179	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLRGYVLGGGTKLTVL	AJOU-78-VL
180	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGYWDYSLSGYVLGGGTKLTVL	AJOU-79-VL
181	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-80-VL
182	QSVLTQPPSASGTPGQRVTISCSGSSANSRTDGFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-86-VL
183	QSVLTQPPSASGTPGQRVTISCSGSAQFGSRDNFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-87-VL
184	QSVLTQPPSASGTPGQRVTISCSGSTKQMHNYQFNWYQQLPGTAPKLLIYADSHRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-88-VL
185	QSVLTQPPSASGTPGQRVTISCSGSLLRGENLQFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-89-VL
186	QSVLTQPPSASGTPGQRVTISCSGSPLFPDSGSFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-90-VL
187	QSVLTQPPSASGTPGQRVTISCSGSAALDLSPSFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-91-VL
188	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGKTNYAQKLQGRVTMTTDTSTTTAYMEMRSLRSDDTAVYYCARGSGYDLDYWG QGTLVSVSS	REGN-VH-3
189	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFWMTWVRQAPGKGLEWVANIKQD GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDPGRTMVRGGIRY YYGMDVWGQGTTVTVSS	REGN-VH-19
190	EVKLAESGGGLVQPGGSLRLSCAASGFTFSSHWMNWVRQAPGKGLEWVANIKQD GSDKYYVDSVKGRFTISRDNAKNSLYLQLNSLIAEDTAVYYCARDRGVRPPRGAFDIW GQGTMVTVSS	REGN-VH-35
191	QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGISWVRQAPGQGLEWMGWIRTY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDEARIVVAGTTP YYYGMDVWGQGTTVTVSS	REGN-VH-51
192	QVQLVESGGGLVQPGGSLRLSCAVSGFTISDHYMSWIRQAPGKGLEWISYISSSGSKI YYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARTRQLVGDYWGQGTLVT VSS	REGN-VH-67
193	EVQLVESGGGLVQPGRSLRLSCAASGFTFDNYAMHWVRQAPGKGLEWVSGIRWN SGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEGGYSGYRPGPFFD YWGQGTLVTVSS	REGN-VH-83
194	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGHTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGSGYDFDSWGQ GTLVTVSS	REGN-VH-99
195	QVQLVQSGAEVKKPGASVKVSCKASRYTFTSYDINWVRQATGQGLEWMGWMNP NSGNTGYAQKFQGRVTMTRNTSTSTAYMELSSLRSEDTAVYYCARVRRFFDYWGQ GTLVTVSS	REGN-VH-115

196	QVQLVQSGPEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGNINYAQKLQGRVTMTTDTSTSTAYMDLRSLRSDDTAVYYCARGSGYDFDYWGQ GTLVTVSS	REGN-VH-147
197	QVQLVQSGAEVKKPGASVKVSCKDSAYTFNRYGISWVRQAPGQGLEWMGWISAY TGNTVYAQKLQGRVTMTTDNSTSTAYMELRSLRSDDTAVYYCARDKSIFGVVRGFD YWGQGTLVTVSS	REGN-VH-163
198	AIQMTQSPSSLSASVGDRVTITCRASQGIRNALGWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTFSSLQPEDFATYYCLQDFNYPYTFGQGTKLEIK	REGN-VL-11
199	DIQMTQSPSSVSASVGDRVTISCRASQGVSSWLAWYQQKPGNAPKLLISAASSIQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPLTFGGGTKVEIK	REGN-VL-27
200	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSFQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPLTFGGGTTVEIK	REGN-VL-43
201	DIQMTQSPSSVSASVGDRVTITCRASQDISIWLAWYQQSPGKAPKLLINVASRLQSG VPSRFSGSGSGTDFTLTINSLQPEDFVTYYCQQANSFPITFGQGTRLATK	REGN-VL-59
202	DIQLTQSPSFLSASVGDRVTITCWASQGISSYLAWYQQKPGKAPKLLIFAASTLQSGV PSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIR	REGN-VL-75
203	EIVMTQSPATLSVSPGERATLSCRASQSVNYNLAWYQHKPGQAPRLLIYGASTRATGI PARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEIK	REGN-VL-91
204	AIQMTQSSSSLSASVGDRVTITCRASQAIRNALGWYQQKPGKAPKVLIYAASSLQSGI PSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYDYPYTFGQGTKLEIK	REGN-VL-107
205	DIQLTQSPSFLSASVGDRVTITCWASQGIISYLAWYQQKPGKAPKLLIYAASTLHSGVP SRFSGSGSGTEFTLTISSLQPEDFATYYCHQLKSYPITFGQGTRLEIK	REGN-VL-123
206	AIQMTQSPSSLSASVGDRVTITCRASQDIRNALGWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSASGTDFTLTISSLQPEDFAAYYCLQDYNYPYTFGQGTKLEIK	REGN-VL-155
207	EIVMTQSPVTLSLSPGERATLPCRASQSVSSSLAWYQQKAGQSPRLLIYGASTRATGI PARFSGSGSGTEFTLTISNLQSEDFAVYYCQQYNNWPLTFGGGTKVEIK	REGN-VL-171
208	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSNGG STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVGYRGGMDVWG QGTTVTVSS	STSA-C27-VH
209	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRSKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-6-33-VH
210	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGVS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVKYRGGMDVWGQ GTTVTVSS	STSA-C27-7-33-VH
211	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTSGS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-24-56-VH
212	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTGTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGAYRGGMDVWGQ GTTVTVSS	STSA-C27-47-56-VH
213	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVAYRGGMDVWGQ GTTVTVSS	STSA-C27-33-33-VH
214	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVLYRGGMDVWGQ GTTVTVSS	STSA-C27-56-56-VH
215	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKSKYRGGMDVWGQ GTTVTVSS	STSA-C27-78-78-VH

216	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISGNSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKLKYRGGMDVWGQG TTVTVSS	STSA-C27-82-58-VH
217	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISHSGTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVRVLYRGGMDVWGQ GTTVTVSS	STSA-C27-54-54-VH
218	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGVS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVKYRGGMDVWGQ GTTVTVSS	STSA-C27-36-36-VH
219	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSNGG STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVFVRYRGGMDVWGQ GTTVTVSS	STSA-C27-53-53-VH
220	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGRYRGGMDVWGQ GTTVTVSS	STSA-C27-67-67-VH
221	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTGGS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGRYRGGMDVWGQ GTTVTVSS	STSA-C27-55-55-VH
222	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISHSGN STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKRRYRGGMDVWGQ GTTVTVSS	STSA-C27-59-59-VH
223	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSNS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-58-58-VH
224	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKPAYRGGMDVWGQ GTTVTVSS	STSA-C27-52-52-VH
225	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISYSSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-Y2-Y2-VH
226	ETTLTQSPDTLPLSPGDRASLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATG VPGRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGSSSVTFGQGTKLEIK	STSA-C27-VL
227	EIVLTQSPGTLSLSPGERATLSCRASQGISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-6-33-VL
228	EIVLTQSPGTLSLSPGERATLSCRASQGISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-7-33-VL
229	EIVLTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-24-56-VL
230	EIVLTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-47-56-VL
231	EIVLTQSPGTLSLSPGERATLSCRASQGISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-33-33-VL
232	EIVLTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-56-56-VL
233	EIVLTQSPGTLSLSPGERATLSCRASQSISTAYLAWYQQKPGQAPRLLIYGTSRRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-78-78-VL
234	EIVLTQSPGTLSLSPGERATLSCRASQDISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-82-58-VL
235	EIVLTQSPGTLSLSPGERATLSCRASQDVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-54-54-VL
236	EIVLTQSPGTLSLSPGERATLSCRASQNISTAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-36-36-VL

237	EIVLTQSPGTLSLSPGERATLSCRASQDASNAYLAWYQQKPGQAPRLLIYGTSRRATG IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGSSSVTFGQGTKLEIK	STSA-C27-53-53-VL
238	EIVLTQSPGTLSLSPGERATLSCRASQGVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGRSSVTFGQGTKLEIK	STSA-C27-67-67-VL
239	EIVLTQSPGTLSLSPGERATLSCRASQNISTAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGTSSVTFGQGTKLEIK	STSA-C27-55-55-VL
240	EIVLTQSPGTLSLSPGERATLSCRASQSVSTAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-59-59-VL
241	EIVLTQSPGTLSLSPGERATLSCRASQDISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-58-58-VL
242	EIVLTQSPGTLSLSPGERATLSCRASQGVSTAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-52-52-VL
243	EIVLPQSPGTLSLSPGERATLSCRASQGVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQL YGSTSVTFGQGTKLEIK	STSA-C27-Y2-Y2-VL
244	EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYGMHWVRQAPGKGLEWVAHIRSKS SNYATYYADSVKDRFTISRDDSQSMLYLQMNNLKTEDTAMYYCVRWFRAMDYWG QGTSVTVSS	Y0188-1 VH
245	EVQLIESGGGLVQPKGSLKLSCAASGFTFNMYAMDWVRQAPGKGLEWVARIRSKG SNFETNYADSVKDRFTISRDDSQSMVYLQMINLKTEDTAMYYCVRHRGGAWFAYW GQGTLVSVSA	Y0188-2 VH
246	QVQLVETGGGLVRPGNSLKLSCVTSGFTFSNYRMHWLRQPPGKRLEWIAVITVKSN NYGANYAESVKGRFAISRDDSKSSVYLEMNRLREEDTATYFCSRERAYGNPFDYWG QGTTLTVSS	Y0188-3 VH
247	EVQLVESGGGLVQPKGSLKLSCAASGFTFNMYAMNWVRQAPGQGLEWVARIRSKS NNYATYYADSVKDRFIISRDDSESMVYLQMSNLRAADTAMYYCVRHLRAMDYWG QGTSVTVSS	Y0188-4 VH
248	EVQLVESGGGLVQPKGSLKLSCAASGFSFNMYAMNWVRQAPGKGLEWVARIRTKS NHYSTYYADSVKDRFTISRDDSASMFYLQMNNLKTEDTAMYFCVRHLRAMDYWG QGTSVTVSS	Y0188-6 VH
249	EVQLIESGGGLVQPKGSLKLSCAASGFTFNMYAMDWVRQAPGKGLEWVARIRSKG SNFETNYADSVKDRFTISRDDSQSMVYLQMNNLKTEDTAMYYCVRHRGGAWFAY WGQGTLVTVSA	Y0188-8 VH
250	EVQLVESGGGLVRPKGSLKLSCAASGFSFNTYAMNWVRQAPGKGLEWIVWIRSKSH NYATYYADSVKDRFTISRDDSESMLYLQMNNLKTEDTAMYYCVRHLRAMDYWGQ GTSVTVSS	Y0188-9 VH
251	EVRLVESGGGLVQPKGSLKLSCEASGFSFNMYAMNWVRQAPGKGLEWITHIRSKSN NYATYYADSVKDRFIISRDDSESMVYLQMNNLKTEDTAMYYCVRLLRALDYWGQGT SVTVSS	Y0188-10 VH
252	EVQLVESGGGLVQPKGSLKLSCAASGFTFNMYGMHWVRQAPGKGLEWVAHIRSKS SNYATYYADSVKDRLTISRDDSQSMLYLQMNNLKTEDTAMYYCVRWFRAMDYWG QGTSVTVSS	Y0188-14 VH
253	EVQLVESGGGLVKPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTTWFRAMDYWGQ GTLVTVSS	HV3-15-14 VH
254	EVQLVESGGGLVQPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVSHIRSKS SNYATYYADSVKDRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARWFRAMDYWGQ GTLVTVSS	HV3-48-14 VH
255	EVQLVESGGGLVQPGGSLKLSCAASGFTFSMYGMHWVRQASGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNTAYLQMNSLKTEDTAVYYCTRWFRAMDYWGQ GTLVTVSS	HV3-73*2-14 VH

256	EVQLVESGGGLVQPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARWFRAMDYWGQ GTLVTVSS	HV3-72-14 VH
257	EVQLVESGGGLVQPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVSHIRSKS SNYATYYADSVKDRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARWFRAMDYWGQ GTLVTVSS	Y01-14 VH
258	EVQLVESGGGLEQPGGSLRLSCAGSGFTFRMYGMHWVRQAPGKGLEWVSHIRSKS SNYATYYADSVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWFRAMDYWGQ GTTVTVSS	162-14 VH
259	EVQLVESGGGLVQPGGSLKLSCAASGFTFSMYGMHWVRQASGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNTAYLQMNSLKTEDTAVYYCTRWFRAMDYWGQ GTTVTVSS	VH73-14 VH
260	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQEKPGQSPKLLIYWASTRHT GVPDRFTGSGSGTDYTLTISSVQAEDLALYYCQQHYSTPLTFGAGTKLELK	Y0188-1 VL
261	DIVVTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNL ESGVPARFSGSGSGTDFTLNIHPVEEEDVAIYYCQHSRELPLTFGAGTKLELK	Y0188-2 VL
262	DIQMTQSPSSLSASLGERVSLTCRASQEISGYLSWLQQKPDGTIKRLIYAASTLDSGVP KRFSGSRSGSDYSLTISSLESEDFADYYCLQYGSYPYTFGGGTKLEIK	Y0188-3 VL
263	DIVLTQSPASLTVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNLE SGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPITFGSGTKLEIK	Y0188-4 VL
264	DIVLTQSPASLVVSLGQRATISCRASQSVSTSGYSYMHWYQQKPGQPPKLLIYLASNV QSGVPARFSGSGSGTDFTLNIHPVEEEDVATYYCHHNRDLPFTFGSGTKLEIK	Y0188-6 VL
265	DIVVTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNL ESGVPARFSGSGSGTDFTLNIHPVEEEDVAIYYCQHSRELPLTFGAGTKLELK	Y0188-8 VL
266	DIVLTQSPASLAVSLGQRATISCRASKSVSASGYSYMHWYQQKPGQPPKLLIYLASNL QSGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPPTFGGGTKLEIK	Y0188-9 VL
267	DIVLTQSPASLAVFLGQRATISCRASKSVSTSGYSYMHWYQQKAGQPPKLLIYLASNL ESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCHHSRELPITFGSGTKLEMK	Y0188-10 VL
268	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQEKPGQSPKLLIYWASTRHT GVPDRFTGSGSGTDYTLTISSVQAEDLALYYCQQHYSTPLTFGAGTKLELK	Y0188-14 VL
269	EIVLTQSPGTLSLSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYWASTRHTGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHYSTPLTFGQGTKVEIK	Y01-14 VL
270	DIVMTQSPLSLPVTPGEPASISCKASQDVSTAVAWYLQKSGQSPQLLIYWASTRHTG VPDRFSGSGSGTDFTLKISRVEAEDVGFYYCQQHYSTPLTFGQGTKLEIK	164-14 VL
271	DIVMTQSPDSLAVSLGERATINCKASQDVSTAVAWYQQKPGQPPKLLIYWASTRHT GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHYSTPLTFGGGTKVEIK	KV4-14 VL
272	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKVPKLLIYWASTRHT GVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQQHYSTPLTFGGGTKVEIK	KV1-27-14 VL
273	DIQLTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYWASTRHTG VPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQHYSTPLTFGGGTKVEIK	KV1-9-14 VL
274	DIQMTQSPSSLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLLYWASTRHT GVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYSTPLTFGGGTKVEIK	KV1-NL1-14 VL
275	AIRMTQSPFSLSASVGDRVTITCKASQDVSTAVAWYQQKPAKAPKLFIYWASTRHTG VPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYSTPLTFGGGTKVEIK	KV1D-43-14 VL

EXAMPLES

[0126] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention.

Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Prevention of Particle Formation in Lipase-Containing Formulations with PEG3350 or Poloxamer 188

[0127] Without intending to be bound by theory, it is believed that a putative phospholipase B-like 2 (PLBL2), which is highly conserved in hamster, rat, mice, human and bovine, copurifies under certain processes with some classes of proteins-of-interest produced in certain cell lines, and has esterase activity responsible for the hydrolysis of polysorbate 20 and 80. As an alternative to removing lipases through purification methods (e.g., as described in US Patent No. 10,342,876), formulations of IL-4R antibody were prepared using alternative surfactants, and particulate formation was measured over time. An anti-IL-4R antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs:1/2 at a concentration of 150 mg/mL of mAb1 was formulated with 20 mM histidine, 12.5 mM sodium acetate, 25 mM arginine-HCl, 5% w/v sucrose, and either PEG3350 or poloxamer 188 at varying concentrations, at pH 5.9. The formulations were stored in syringes at 5°C for up to 36 months with periodic measurements taken of the number of particles (≥10 µm and ≥25 µm) present in the formulations, as determined by microscopy.

[0128] As shown in Fig. 1, few particles of ≥10 µm or ≥25 µm were identified in the formulations over the 36 month observation period. Moreover, no appreciable differences or changes in the number of subvisible particles among the different PEG3350- or poloxamer 188-containing formulations were observed over the course of the storage period. This experiment demonstrates that low concentrations of PEG3350 or poloxamer 188 can prevent particle formulation over long storage periods.

Example 2: Agitation Stress Stability of Formulations Containing PEG3350 or Poloxamer 188

[0129] The agitation stress stability was tested for IL-4R antibody formulations containing different concentrations of the surfactant PEG3350 or poloxamer 188. An anti-IL-4R antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs:1/2 at a concentration of 150 mg/mL was formulated with 20 mM histidine, 12.5 mM sodium acetate, 25 mM arginine-HCl, 5% w/v sucrose, and PEG3350 or poloxamer 188 at varying concentrations, at pH 5.9. The formulations were stored in glass vials and agitated by vortexing (speed setting = 4) for 30 minutes, 60 minutes, or 120

minutes. The percentage of high molecular weight (HMW) species was then determined by size exclusion ultra high performance liquid chromatography (SE-UPLC).

[0130] As shown in Fig. 2A, formulation of the antibody with at least 0.01% (w/v) PEG3350 prevented an observable increase of HMW species (quantitated by SE-UHPLC) due to the agitation. Lower amounts of PEG3350 (0.001% or 0.005%) were insufficient to prevent formation of HMW. Similarly, as shown in Fig. 2B, formulation of the antibody with at least 0.01% (w/v) poloxamer 188 prevented an observable increase of HMW species but HMW species were observed with lower amounts of poloxamer 188 (0.001% or 0.005%).

Example 3: Thermal Stress Stability of Formulations Containing PEG3350 or Poloxamer 188

[0131] The thermal stress stability of IL-4R antibody formulations containing PEG3350 or poloxamer 188 was tested and compared to various IL-4R antibody formulations containing polysorbate. An anti-IL-4R antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs:1/2 at a concentration of 150 mg/mL was formulated with 20 mM histidine, 12.5 mM sodium acetate, 25 mM arginine-HCl, 5% w/v sucrose, and polysorbate 20, polysorbate 80, PEG3350 or poloxamer 188 at varying concentrations, at pH 5.9. These formulations were subjected to thermal stress (45°C) for a period of up to 56 days, and the percentage of high molecular weight (HMW) species was determined by size exclusion ultra high performance liquid chromatography (SE-UPLC) at 7 days, at 14 days, at 28 days, at 42 days, and at 56 days.

[0132] As shown in Fig. 3, antibody formulations comprising PEG3350 or poloxamer 188 at a concentration of 0.01% or 0.02% showed similar thermal stability to antibody formulations containing lower amounts of polysorbate (up to 0.1% w/v). By 28 days, the PEG3350- or poloxamer 188-containing formulations exhibited a lower percentage of HMW species than control formulations comprising 0.2% polysorbate 20.

Example 4: Thermal Stress Stability of Formulations Containing Varying Concentrations of Poloxamer 188 or PEG3350

[0133] The thermal stress stability of IL-4R antibody formulations containing different concentrations of poloxamer 188 or PEG3350 was tested under thermal stress conditions (45°C) for up to 3 months. An anti-IL-4R antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs:1/2 at a concentration of 150 mg/mL was formulated with 20 mM histidine, 12.5 mM sodium acetate, 25 mM arginine-HCl, 5% w/v sucrose, and surfactant [polysorbate 80 at 0.2% w/v, poloxamer 188 at 0.01%, 0.1%, or 0.5% w/v, or PEG3350 at 0.01%, 0.1%, or 0.5% w/v] at pH 5.9. These formulations were stored in glass vials at 45°C for 1, 2, or 3 months. The percentage of drug product (antibody) recovered was determined by reverse phase ultra high performance liquid

chromatography (RP-UPLC). The percentage of high molecular weight (HMW) species was determined by size exclusion ultra high performance liquid chromatography (SE-UPLC). The formation of charge variant species was measured by cation exchange ultra performance liquid chromatography (CEX-UPLC). Micro-flow imaging (MFI) was used to measure subvisible particles.

[0134] Table 2 shows stability data for a formulation containing 0.2% (w/v) polysorbate 80 at 0, 1, and 3 months. Tables 3, 4, and 5 show stability data for formulations containing 0.01%, 0.1%, and 0.5% poloxamer 188, respectively. Tables 6, 7, and 8 show stability data for formulations containing 0.01%, 0.1%, and 0.5% PEG3350, respectively. As shown in Tables 3 and 6, even the lowest tested concentrations of poloxamer 188 and PEG3350 (0.01%) provided a similar degree of protection as 0.2% polysorbate 80. The 0.01% poloxamer 188 formulation exhibited similar stability characteristics as 0.1% and 0.5% poloxamer 188 (see, Tables 3-5). The 0.01% PEG3350 formulation exhibited similar stability characteristics as 0.1% and 0.5% PEG3350 (see, Tables 6-8).

Table 2: Stability Data for Formulation with 0.2% (w/v) Polysorbate 80

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	98	94
Purity by SE-UPLC	% HMW	2.1	10.3	26.6
	% Main	97.2	88.7	70.7
	% LMW	0.7	1.0	2.7
Charge Variant Analysis by CEX-UPLC	% Acidic	27.7	53.7	86.9
	% Main	62.5	41.0	9.5
	% Basic	9.9	5.3	3.6
MFI (# particles/mL)	2-10 µm	125	1428	377
	≥10 µm	23	29	19
	≥25 µm	4	2	4

Table 3: Stability Data for Formulation with 0.01% (w/v) Poloxamer 188

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	100	98
Purity by SE-UPLC	% HMW	2.1	9.1	23.7
	% Main	97.2	90.0	73.5
	% LMW	0.7	0.9	2.7
Charge Variant Analysis by CEX-UPLC	% Acidic	28.4	51.7	86.6
	% Main	62.1	43.1	8.9
	% Basic	9.5	5.3	4.5
MFI (# particles/mL)	2-10 µm	79	142	396
	≥10 µm	17	17	8
	≥25 µm	0	6	0

Table 4: Stability Data for Formulation with 0.1% (w/v) Poloxamer 188

Assay	Length of Storage at 45°C (months)

		0	1	3
% of Antibody Recovered by RP-UPLC		100	99	100
Purity by SE-UPLC	% HMW	2.1	9.1	23.7
	% Main	97.3	90.0	73.6
	% LMW	0.6	0.9	2.8
Charge Variant Analysis by CEX-UPLC	% Acidic	28.1	51.9	84.0
	% Main	62.1	46.2	8.7
	% Basic	9.8	1.9	7.4
MFI (# particles/mL)	2-10 µm	69	540	811
	≥10 µm	0	17	25
	≥25 µm	0	0	0

Table 5: Stability Data for Formulation with 0.5% (w/v) Poloxamer 188

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	100	100
Purity by SE-UPLC	% HMW	2.1	9.1	24.2
	% Main	97.3	90.0	73.1
	% LMW	0.6	0.9	2.7
Charge Variant Analysis by CEX-UPLC	% Acidic	29.5	50.8	86.6
	% Main	61.5	44.5	9.0
	% Basic	9.1	4.8	4.4
MFI (# particles/mL)	2-10 µm	179	805	1887
	≥10 µm	10	8	307
	≥25 µm	0	2	61

Table 6: Stability Data for Formulation with 0.01% (w/v) PEG3350

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	102	100
Purity by SE-UPLC	% HMW	2.1	9.3	23.6
	% Main	97.4	89.9	73.6
	% LMW	0.6	0.9	2.7
Charge Variant Analysis by CEX-UPLC	% Acidic	29.4	51.6	86.4
	% Main	62.2	46.1	11.9
	% Basic	8.5	2.4	1.8
MFI (# particles/mL)	2-10 µm	42	494	2085
	≥10 µm	6	15	206
	≥25 µm	0	6	40

Table 7: Stability Data for Formulation with 0.1% (w/v) PEG3350

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	97	92
Purity by SE-UPLC	% HMW	2.1	9.3	22.4
	% Main	97.4	89.8	74.9
	% LMW	0.6	0.9	2.8
	% Acidic	32.1	51.0	85.7

Charge Variant Analysis by CEX-UPLC	% Main	60.6	45.6	10.9
	% Basic	7.4	3.4	3.5
MFI (# particles/mL)	2-10 µm	94	313	2058
	≥10 µm	2	15	159
	≥25 µm	0	4	21

Table 8: Stability Data for Formulation with 0.5% (w/v) PEG3350

Assay		Length of Storage at 45°C (months)		
		0	1	3
% of Antibody Recovered by RP-UPLC		100	100	98
Purity by SE-UPLC	% HMW	2.1	9.2	23.9
	% Main	97.3	89.8	73.4
	% LMW	0.6	0.9	2.7
Charge Variant Analysis by CEX-UPLC	% Acidic	29.7	52.0	83.6
	% Main	62.0	45.7	10.5
	% Basic	8.4	2.3	6.0
MFI (# particles/mL)	2-10 µm	121	1289	2654
	≥10 µm	0	44	279
	≥25 µm	0	25	31

Example 5: Stability Data for Storage and Stress Conditions for Formulations Containing Varying Concentrations of Poloxamer 188 or PEG3350

[0135] The stability of IL-4R antibody formulations in having varying concentrations of poloxamer 188 or PEG3350 was tested under storage conditions of 5°C for up to 18 months, accelerated conditions (25°C for up to 6 months), thermal stress conditions (45°C for up to 2 months), and agitation stress conditions. An anti-IL-4R antibody comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs:1/2 at a concentration of 150 mg/mL was formulated with 20 mM histidine, 12.5 mM sodium acetate, 25 mM arginine-HCl, and 5% w/v sucrose, either in the absence of surfactant or in the presence of poloxamer 188 or PEG3350 at 0.02%, 0.04%, or 0.1% w/v, at pH 5.9. These formulations were stored in Nuova Ompi 2.25mL syringes. The percentage of HMW species was determined by SE-UPLC. The formation of charge variant species was measured by CEX-UPLC. Membrane microscopy and/or MFI was used to measure the number of particles in the container.

[0136] Tables 9-11 show data for a formulation without surfactant. Tables 12-14, 15-17, and 18-20 show stability data for formulations containing 0.02%, 0.04%, and 0.1% (w/v) poloxamer 188, respectively. Tables 21-23, 24-26, and 27-29 show stability data for formulations containing 0.02%, 0.04%, and 0.1% (w/v) PEG3350, respectively. As shown in Tables 12, 15, and 18, formulations containing 0.02%, 0.04%, or 0.1% (w/v) poloxamer had significantly fewer particles after prolonged storage at 5°C (up to 18 months). Similarly, as shown in Tables 21, 24, and 27, formulations

containing 0.02%, 0.04%, or 0.1% PEG3350 had significantly fewer particles after prolonged storage at 5°C (up to 18 months). Under accelerated conditions of 25°C or thermal stress conditions of 45°C, formulations containing 0.02%, 0.04%, or 0.1% (w/v) poloxamer 188 or PEG3350 had significantly fewer subvisible particles than a formulation without surfactant (see, Tables 10, 13, 16, 19, 22, 25, and 28).

[0137] The formulations were subjected to agitation stress for 24 hours at 25°C, then stored as follows: at 5°C for 6, 12,or 18 months, at 25°C for 6 months, or at 45°C for 1 or 2 months. Formulations containing 0.02%, 0.04%, or 0.1% (w/v) poloxamer 188 or PEG3350 had a significantly less formation of HMW species after 24 hours of agitation at 25°C, as compared to a formulation lacking surfactant. Additionally, the formulations containing 0.02%, 0.04%, or 0.1% (w/v) poloxamer 188 or PEG3350 exhibited lower percentages of HMW species for 24 hours of agitation followed by prolonged storage at 5°C or 25°C conditions, as compared to a formulation lacking surfactant, indicative of improved stability. See, Tables 11, 14, 17, 20, 23, 26, and 29.

Table 9: Storage Stability Data (5°C) for Formulation Without Surfactant

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.1	2.2	2.3	2.6	2.6	2.7	2.9
	% Main	96.8	97.6	97.7	96.5	96.5	96.6	96.3
	% LMW	1.1	0.3	0.0	1.0	0.9	0.7	0.9
Charge Variant Analysis by CEX-UPLC	% Acidic	27.1	26.2	25.8	26.4	N/A	26.3	25.7
	% Main	58.7	61.1	61.8	60.4	N/A	60.8	61.9
	% Basic	14.2	12.7	12.4	13.3	N/A	13.0	12.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	72	N/A	51	120
	≥ 25 µm	N/A	N/A	N/A	11	N/A	30	27
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	13600	N/A	N/A	17782	N/A	15175	38790
	5-300µm	4895	N/A	N/A	6367	N/A	4859	17738
	10-300µm	2491	N/A	N/A	3024	N/A	2044	9521
	25-300µm	533	N/A	N/A	511	N/A	406	2368
	50-300µm	47	N/A	N/A	59	N/A	51	265

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 10: Accelerated Storage and Thermal Stress Stability Data for Formulation Without Surfactant

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.1	2.7	3.2	3.8	3.6	4.7	8.3
	% Main	96.8	96.9	96.38	94.9	95.4	93.8	89.3
	% LMW	1.1	0.4	0.0	1.3	1.0	1.5	2.4
Charge Variant Analysis by CEX-UPLC	% Acidic	27.1	26.5	28.9	32.3	31.2	37.5	62.5
	% Main	58.7	59.5	57.9	53.8	56.3	50.3	27.0
	% Basic	14.2	14.1	13.2	13.9	12.5	12.2	10.5
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	49	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	11	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	13600	N/A	N/A	19813	N/A	9066	N/A
	5-300µm	4895	N/A	N/A	8827	N/A	2510	N/A
	10-300µm	2491	N/A	N/A	4347	N/A	1117	N/A
	25-300µm	533	N/A	N/A	639	N/A	163	N/A
	50-300µm	47	N/A	N/A	39	N/A	7	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 11: Agitation Stress Stability Data for Formulation Without Surfactant

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.1	9.4	8.5	9.1	7.2	7.9	5.3	8.3
	% Main	96.8	90.6	90.6	90.3	92.0	91.1	93.4	89.5
	% LMW	1.1	0.0	0.9	0.6	0.8	1.0	1.3	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	27.1	26.7	25.8	26.4	26.2	32.4	37.5	61.5
	% Main	58.7	59.8	61.0	60.7	61.8	53.9	49.9	26.8
	% Basic	14.2	13.5	13.3	13.0	12.1	13.7	12.7	11.7

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

Table 12: Storage Stability Data (5°C) for Formulation with 0.02% (w/v) Poloxamer 188

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.0	2.2	2.3	2.5	2.6	2.7	2.8

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
	% Main	97.1	97.6	97.7	96.5	96.5	96.6	96.4
	% LMW	0.8	0.2	0.0	1.0	0.9	0.7	0.9
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	27.5	26.4	26.5	N/A	26.1	25.9
	% Main	58.4	59.2	60.5	59.9	N/A	60.3	61.8
	% Basic	14.8	13.3	13.1	13.6	N/A	13.6	12.3
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	36	N/A	42	86
	≥ 25 µm	N/A	N/A	N/A	17	N/A	17	21
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	27602	N/A	N/A	6120	N/A	14265	9781
	5-300µm	8871	N/A	N/A	992	N/A	3355	1560
	10-300µm	3440	N/A	N/A	277	N/A	1349	622
	25-300µm	294	N/A	N/A	10	N/A	201	43
	50-300µm	11	N/A	N/A	2	N/A	38	2

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 13: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.02% (w/v) Poloxamer 188

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Visual Appearance								
Purity by SE-UPLC	% HMW	2.0	2.7	3.1	3.8	3.8	4.8	8.2
	% Main	97.1	97.1	96.9	95.1	95.1	93.8	89.1
	% LMW	0.8	0.3	0.0	1.2	1.1	1.4	2.6
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.8	29.2	32.1	31.5	37.9	60.0
	% Main	58.4	59.0	55.4	54.3	55.3	49.1	26.6
	% Basic	14.8	14.2	15.4	13.6	13.3	13.0	13.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	36	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	13	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	27602	N/A	N/A	5786	N/A	4584	N/A
	5-300µm	8871	N/A	N/A	457	N/A	455	N/A
	10-300µm	3440	N/A	N/A	198	N/A	209	N/A
	25-300µm	294	N/A	N/A	10	N/A	14	N/A
	50-300µm	11	N/A	N/A	2	N/A	0	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 14: Agitation Stress Stability Data for Formulation with 0.02% (w/v) Poloxamer 188

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.0	4.1	3.0	3.0	3.0	3.9	4.9	8.3
	% Main	97.1	95.7	96.1	96.3	95.9	95.0	93.8	89.3
	% LMW	0.8	0.1	0.9	0.7	0.9	1.2	1.4	2.5
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.7	26.0	26.2	25.8	32.5	37.4	59.4
	% Main	58.4	59.3	60.8	60.1	61.6	53.6	48.9	26.9
	% Basic	14.8	14.0	13.3	13.8	12.6	13.9	13.7	13.7

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 15: Storage Stability Data (5°C) for Formulation with 0.04% (w/v) Poloxamer 188

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.1	2.2	2.3	2.6	2.6	2.7	2.8
	% Main	97.1	97.6	97.7	96.5	96.5	96.6	96.3
	% LMW	0.8	0.2	0.0	1.0	0.9	0.7	0.8
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	27.7	26.4	26.1	N/A	25.9	25.6
	% Main	58.3	59.0	60.3	59.4	N/A	60.8	62.0
	% Basic	14.8	13.4	13.3	14.5	N/A	13.3	12.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	34	N/A	25	40
	≥ 25 µm	N/A	N/A	N/A	2	N/A	8	4
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	7067	N/A	N/A	2747	N/A	15777	19227
	5-300µm	772	N/A	N/A	171	N/A	1698	2034
	10-300µm	289	N/A	N/A	54	N/A	734	720
	25-300µm	8	N/A	N/A	5	N/A	33	23
	50-300µm	0	N/A	N/A	0	N/A	3	0

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 16: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.04% (w/v) Poloxamer 188

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.1	2.7	2.9	3.8	3.8	4.8	8.7
	% Main	97.1	97.2	97.1	95.0	95.2	93.7	89.0
	% LMW	0.8	0.1	0.0	1.1	1.0	1.5	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.4	29.5	32.3	31.3	37.8	60.3
	% Main	58.3	57.9	54.8	54.1	55.6	48.5	24.2
	% Basic	14.8	15.6	15.8	13.6	13.0	13.8	15.5
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	15	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	0	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	7067	N/A	N/A	7042	N/A	7510	N/A
	5-300µm	772	N/A	N/A	550	N/A	377	N/A
	10-300µm	289	N/A	N/A	253	N/A	98	N/A
	25-300µm	8	N/A	N/A	5	N/A	3	N/A
	50-300µm	0	N/A	N/A	2	N/A	0	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 17: Agitation Stress Stability Data for Formulation with 0.04% (w/v) Poloxamer 188

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.1	2.0	2.6	2.8	2.9	3.9	5.0	8.8
	% Main	97.1	95.2	96.5	96.5	96.2	95.0	93.7	89.0
	% LMW	0.8	2.7	0.1	0.7	0.9	1.2	1.3	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.9	26.3	26.4	26.3	32.3	38.0	60.2
	% Main	58.3	58.3	60.0	59.9	61.2	54.3	48.3	25.4
	% Basic	14.8	14.8	13.7	13.7	12.6	13.4	13.8	14.4

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

Table 18: Storage Stability Data (5°C) for Formulation with 0.1% (w/v) Poloxamer 188

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.1	2.2	2.3	2.6	2.6	2.7	2.9

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
	% Main	97.0	97.6	97.8	96.5	96.5	96.6	96.3
	% LMW	1.0	0.2	0.0	0.9	0.9	0.7	0.9
Charge Variant Analysis by CEX-UPLC	% Acidic	27.0	27.6	26.2	26.0	N/A	26.3	25.3
	% Main	58.2	59.1	59.9	59.8	N/A	60.7	62.3
	% Basic	14.8	13.3	14.0	14.2	N/A	13.0	12.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	84	N/A	34	114
	≥ 25 µm	N/A	N/A	N/A	19	N/A	4	30
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	3424	N/A	N/A	3325	N/A	6985	18856
	5-300µm	215	N/A	N/A	217	N/A	426	1802
	10-300µm	119	N/A	N/A	131	N/A	204	894
	25-300µm	5	N/A	N/A	3	N/A	8	16
	50-300µm	0	N/A	N/A	2	N/A	3	3

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 19: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.1% (w/v) Poloxamer 188

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.1	2.7	3.0	3.8	3.8	4.7	8.3
	% Main	97.0	97.2	97.0	95.0	95.2	94.0	89.4
	% LMW	1.0	0.1	0.0	1.2	1.0	1.3	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	27.0	27.6	29.5	32.3	31.4	37.8	59.4
	% Main	58.2	57.8	54.3	53.8	54.9	49.0	25.9
	% Basic	14.8	14.6	16.3	13.9	13.7	13.3	14.7
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	38	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	8	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	3424	N/A	N/A	18633	N/A	7812	N/A
	5-300µm	215	N/A	N/A	1410	N/A	465	N/A
	10-300µm	119	N/A	N/A	650	N/A	204	N/A
	25-300µm	5	N/A	N/A	29	N/A	5	N/A
	50-300µm	0	N/A	N/A	0	N/A	0	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 20: Agitation Stress Stability Data for Formulation with 0.1% (w/v) Poloxamer 188

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.1	2.1	2.6	2.8	2.9	3.9	4.9	8.4
	% Main	97.0	97.8	96.4	96.5	96.3	95.0	93.8	89.2
	% LMW	1.0	0.1	1.0	0.7	0.9	1.2	1.3	2.4
Charge Variant Analysis by CEX-UPLC	% Acidic	27.0	26.8	26.6	26.4	26.4	32.3	38.1	58.9
	% Main	58.2	58.0	60.0	60.3	60.6	54.0	47.5	26.6
	% Basic	14.8	15.2	13.4	13.4	13.0	13.7	14.4	14.5

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

Table 21: Storage Stability Data (5°C) for Formulation with 0.02% (w/v) PEG3350

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.0	2.2	2.3	2.5	2.7	2.7	2.8
	% Main	97.1	97.8	97.7	96.5	96.5	96.6	96.3
	% LMW	0.9	0.0	0.0	0.9	0.9	0.7	0.9
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	25.7	25.9	25.9	N/A	26.1	26.0
	% Main	58.5	61.3	60.4	60.7	N/A	60.5	61.8
	% Basic	14.6	13.0	13.7	13.5	N/A	13.3	12.2
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	15	N/A	23	25
	≥ 25 µm	N/A	N/A	N/A	0	N/A	6	8
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	15027	N/A	N/A	10791	N/A	23589	22239
	5-300µm	6840	N/A	N/A	2297	N/A	8189	6644
	10-300µm	3540	N/A	N/A	1021	N/A	3571	2581
	25-300µm	612	N/A	N/A	144	N/A	444	386
	50-300µm	18	N/A	N/A	8	N/A	18	51

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 22: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.02% (w/v) PEG3350

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.0	2.6	3.1	3.8	3.7	4.9	8.6
	% Main	97.1	97.1	96.9	95.0	95.4	93.8	89.2
	% LMW	0.9	0.3	0.0	1.3	0.9	1.4	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	27.0	29.4	32.3	31.2	37.5	60.9
	% Main	58.5	58.6	55.3	53.8	56.3	50.0	25.7
	% Basic	14.6	14.4	15.3	13.9	12.5	12.5	13.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	49	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	15	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	15027	N/A	N/A	6011	N/A	9876	N/A
	5-300µm	6840	N/A	N/A	2448	N/A	1077	N/A
	10-300µm	3540	N/A	N/A	10334	N/A	432	N/A
	25-300µm	612	N/A	N/A	70	N/A	47	N/A
	50-300µm	18	N/A	N/A	3	N/A	2	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 23: Agitation Stress Stability Data for Formulation with 0.02% (w/v) PEG3350

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Visual Appearance									
Purity by SE-UPLC	% HMW	2.0	2.9	2.9	2.8	2.9	3.9	4.9	8.5
	% Main	97.1	97.1	96.1	96.5	96.2	95.0	93.7	89.1
	% LMW	0.9	0.0	1.0	0.7	0.9	1.1	1.4	2.4
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.7	26.0	261	26.1	32.7	37.6	60.3
	% Main	58.5	59.3	60.7	60.4	61.6	54.0	49.6	25.8
	% Basic	14.6	14.0	13.3	13.6	12.3	13.4	12.8	13.9

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

Table 24: Storage Stability Data (5°C) for Formulation with 0.04% (w/v) PEG3350

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.1	2.2	2.4	2.6	2.6	2.7	2.9
	% Main	97.0	97.7	97.6	96.4	96.5	96.6	96.3
	% LMW	1.0	0.1	0.0	1.0	0.9	0.7	0.9
Charge Variant Analysis by CEX-UPLC	% Acidic	26.8	26.2	25.8	26.4	N/A	26.1	25.2
	% Main	58.2	60.2	61.1	60.4	N/A	60.7	62.7
	% Basic	14.9	13.7	13.1	13.2	N/A	13.2	12.1
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	38	N/A	61	42
	≥ 25 µm	N/A	N/A	N/A	11	N/A	19	6
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	43797	N/A	N/A	18903	N/A	16022	22243
	5-300µm	6840	N/A	N/A	5833	N/A	4553	6873
	10-300µm	10262	N/A	N/A	1951	N/A	1881	3082
	25-300µm	940	N/A	N/A	67	N/A	204	367
	50-300µm	16	N/A	N/A	5	N/A	2	15

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 25: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.04% (w/v) PEG3350

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.1	2.6	3.0	3.8	3.8	4.6	8.2
	% Main	97.0	97.3	97.0	95.1	95.2	94.0	89.4
	% LMW	1.0	0.1	0.0	1.1	1.0	1.4	2.4
Charge Variant Analysis by CEX-UPLC	% Acidic	26.8	27.0	28.8	32.3	31.3	35.3	60.3
	% Main	58.2	58.3	56.0	53.6	55.0	51.1	24.3
	% Basic	14.9	14.8	15.2	14.1	13.7	13.6	15.4
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	80	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	25	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	43797	N/A	N/A	13611	N/A	5744	N/A
	5-300µm	6840	N/A	N/A	3628	N/A	475	N/A
	10-300µm	10262	N/A	N/A	1581	N/A	188	N/A
	25-300µm	940	N/A	N/A	103	N/A	18	N/A
	50-300µm	16	N/A	N/A	2	N/A	2	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 26: Agitation Stress Stability Data for Formulation with 0.04% (w/v) PEG3350

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.1	2.1	2.6	2.7	2.9	3.9	4.8	8.3
	% Main	97.0	97.9	96.4	96.6	96.3	95.0	93.7	89.5
	% LMW	1.0	0.0	1.0	0.7	0.9	1.1	1.5	2.2
Charge Variant Analysis by CEX-UPLC	% Acidic	26.8	26.8	26.6	26.3	25.9	32.6	35.8	59.5
	% Main	58.2	57.5	60.0	60.3	61.7	53.7	50.0	26.4
	% Basic	14.9	15.8	13.5	13.4	12.4	13.6	14.2	14.2

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

Table 27: Storage Stability Data (5°C) for Formulation with 0.1% (w/v) PEG3350

Assay		t=0	Length of Storage at 5 °C (months)					
			1	3	6	9	12	18
Purity by SE-UPLC	% HMW	2.0	2.2	2.3	2.6	2.6	2.7	2.9
	% Main	97.0	97.7	97.7	96.5	96.5	96.6	96.3
	% LMW	0.9	0.2	0.0	0.9	0.9	0.7	0.8
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	27.7	26.5	26.3	N/A	26.3	26.1
	% Main	58.2	59.1	60.0	59.5	N/A	60.4	61.8
	% Basic	15.0	13.3	13.5	14.2	N/A	13.3	12.1
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	99	N/A	36	38
	≥ 25 µm	N/A	N/A	N/A	42	N/A	11	11
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	12061	N/A	N/A	12946	N/A	8967	11449
	5-300µm	1075	N/A	N/A	1010	N/A	528	638
	10-300µm	445	N/A	N/A	414	N/A	184	200
	25-300µm	13	N/A	N/A	16	N/A	2	7
	50-300µm	0	N/A	N/A	0	N/A	0	0

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 28: Accelerated Storage and Thermal Stress Stability Data for Formulation with 0.1% (w/v) PEG3350

Assay		t=0	Length of Incubation at 25 °C (months)			Length of Incubation at 45 °C(months)		
			1	3	6	0.5	1	2
Purity by SE-UPLC	% HMW	2.0	2.7	3.0	3.8	3.7	4.8	8.6
	% Main	97.0	97.1	97.0	95.0	95.3	93.7	88.9
	% LMW	0.9	0.2	0.0	1.2	1.0	1.5	2.5
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	27.7	28.7	32.3	31.1	37.6	60.1
	% Main	58.2	57.1	55.5	53.6	55.4	48.5	26.2
	% Basic	15.0	15.2	15.7	14.1	13.4	13.9	13.7
Membrane Microscopy (# particles/container) [a]	≥ 10 µm	N/A	N/A	N/A	27	N/A	N/A	N/A
	≥ 25 µm	N/A	N/A	N/A	2	N/A	N/A	N/A
MFI (# particles/ container) (aspect ratio ≤ 0.85 applied)	2-300µm	12061	N/A	N/A	6177	N/A	3701	N/A
	5-300µm	1075	N/A	N/A	430	N/A	297	N/A
	10-300µm	445	N/A	N/A	161	N/A	129	N/A
	25-300µm	13	N/A	N/A	7	N/A	15	N/A
	50-300µm	0	N/A	N/A	2	N/A	0	N/A

[a] Microscopy USP specifications: ≥10 µm sizes ≤ 3000 particles/container; ≥25 µm sizes ≤ 300 particles/container

HMW = high molecular weight; LMW = low molecular weight; N/A = not available

Table 29: Agitation Stress Stability Data for Formulation with 0.1% (w/v) PEG3350

Assay		t=0	24 hours agitation*, then storage at 5°C (months)				24 hours agitation*, then storage at 25°C (months)	24 hours agitation*, then storage at 45°C (months)	
			T0	6	12	18	6	1	2
Purity by SE-UPLC	% HMW	2.0	2.1	2.6	2.8	2.9	3.9	5.0	8.8
	% Main	97.0	97.9	96.4	96.5	96.3	95.0	93.7	88.9
	% LMW	0.9	0.0	1.0	0.7	0.9	1.1	1.3	2.3
Charge Variant Analysis by CEX-UPLC	% Acidic	26.9	26.7	26.2	27.2	25.5	32.6	37.7	60.6
	% Main	58.2	57.8	60.0	59.3	62.1	53.7	49.7	25.0
	% Basic	15.0	15.5	13.7	13.5	12.4	13.6	12.7	14.5

* Agitation for 24 hours at 25°C followed by storage at indicated temperature

HMW = high molecular weight; LMW = low molecular weight

[0138] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will

become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Table 30: Sequences Excluded from ST.26-Formatted Sequence Listing

SEQ ID NO:	Sequence
7	LGS

****

What is claimed is:

1. A stable liquid pharmaceutical formulation comprising:

(i) a human antibody that specifically binds to human interleukin-4 receptor alpha (hIL-4Rα);

(ii) one or more buffers;

(iii) a thermal stabilizer;

(iv) a viscosity modifier; and

(v) a surfactant comprising a polyethylene glycol or a poloxamer at a concentration of from 0.01% w/v to 0.19% w/v,

wherein the formulation has a pH of from 5.7 to 6.1.

2. The stable liquid pharmaceutical formulation of claim 1, wherein the antibody comprises a heavy chain variable region (HCVR) comprising complementarity determining regions HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable region (LCVR) comprising complementarity determining regions LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively.

3. The stable liquid pharmaceutical formulation of claim 2, wherein the antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1, and a LCVR comprising the amino acid sequence of SEQ ID NO: 2.

4. The stable liquid pharmaceutical formulation of any one of claims 1 to 3, wherein the antibody has a human IgG heavy chain constant region.

5. The stable liquid pharmaceutical formulation of claim 4, wherein the heavy chain constant region is of isotype IgG1.

6. The stable liquid pharmaceutical formulation of claim 4, wherein the heavy chain constant region is of isotype IgG4.

7. The stable liquid pharmaceutical formulation of any one of claims 1 to 3, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

8. The stable liquid pharmaceutical formulation of any one of claims 1-7, wherein the surfactant is a polyethylene glycol.

9. The stable liquid pharmaceutical formulation of claim 8, wherein the polyethylene glycol is PEG3350.

10. The stable liquid pharmaceutical formulation of any one of claims 1-7, wherein the surfactant is a poloxamer.

11. The stable liquid pharmaceutical formulation of claim 10, wherein the poloxamer is poloxamer 188.

12. The stable liquid pharmaceutical formulation of any one of claims 1-11, wherein the buffer comprises an acetate buffer and/or a histidine buffer.

13. The stable liquid pharmaceutical formulation of claim 12, wherein the buffer comprises acetate at a concentration of from 10 mM to 15 mM.

14. The stable liquid pharmaceutical formulation of claim 13, wherein the acetate is present at a concentation of 12.5 mM ± 1.25 mM.

15. The stable liquid pharmaceutical formulation of claim 12, wherein the buffer comprises histidine at a concentration of from 15 mM to 25 mM.

16. The stable liquid pharmaceutical formulation of claim 15, wherein the histidine is present at a concentration of 20 mM ± 2 mM.

17. The stable liquid pharmaceutical formulation of any one of claims 1-16, wherein the thermal stabilizer is sucrose at a concentration of from 2.5% w/v to 7.5% w/v.

18. The stable liquid pharmaceutical formulation of claim 17, wherein the sucrose is present at a concentration of 5% w/v ± 0.5% w/v.

19. The stable liquid pharmaceutical formulation of any one of claims 1-18, wherein the viscosity modifier is arginine at a concentration of from 20 mM to 80 mM.

20. The stable liquid pharmaceutical formulation of claim 19, wherein the arginine is present at a concentration of 25 mM ± 2.5 mM.

21. The stable liquid pharmaceutical formulation of claim 19, wherein the arginine is present at a concentration of 50 mM ± 2.5 mM.

22. The stable liquid pharmaceutical formulation of claim 19, wherein the arginine is present at a concentration of 75 mM ± 2.5 mM.

23. The stable liquid pharmaceutical formulation of any one of claims 1-22, wherein the antibody is present at a concentration up to 200 mg/mL.

24. The stable liquid pharmaceutical formulation of any one of claims 1-23, wherein the antibody is present at a concentration of from 100 mg/mL to 200 mg/mL.

25. The stable liquid pharmaceutical formulation of claim 24, wherein the antibody is present at a concentration of 150 mg/mL ± 15 mg/mL.

26. The stable liquid pharmaceutical formulation of claim 24, wherein the antibody is present at a concentration of 175 mg/mL ± 15 mg/mL.

27. A stable liquid pharmaceutical formulation comprising:

(i) a human antibody at a concentration of 150 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2;

(ii) acetate at a concentation of 12.5 mM ± 1.25 mM;

(iii) histidine at a concentration of 20 mM ± 2 mM;

(iv) sucrose at a concentration of 5% w/v ± 0.5% w/v;

(v) arginine at a concentration of 25 mM ± 2.5 mM; and

(vi) a surfactant comprising PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v,

wherein the formulation has a pH of 5.9 ± 0.2.

28. A stable liquid pharmaceutical formulation comprising:

(i) a human antibody at a concentration of 175 mg/mL ± 10 mg/mL, wherein the antibody specifically binds to human interleukin-4 receptor alpha (hIL-4Rα) and comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1, and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2;

(ii) acetate at a concentation of 12.5 mM ± 1.25 mM;

(iii) histidine at a concentration of 20 mM ± 2 mM;

(iv) sucrose at a concentration of 5% w/v ± 0.5% w/v;

(v) arginine at a concentration of 25 mM ± 2.5 mM; and

(vi) a surfactant comprising PEG3350 or poloxamer 188 at a concentration of from 0.01% w/v to 0.19% w/v,

wherein the formulation has a pH of 5.9 ± 0.2.

29. The stable liquid pharmaceutical formulation of claim 27 or 28, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9, and a light chain comprising the amino acid sequence of SEQ ID NO: 10.

30. The stable liquid pharmaceutical formulation of any one of claims 1-29, wherein the formulation contains a phospholipase protein.

31. The stable liquid pharmaceutical formulation of any one of claims 1-30, wherein the formulation comprises no more than 3% high molecular weight (HMW) species following agitation by vortexing for up to 120 minutes at room temperature, as determined by size exclusion-ultra performance liquid chromatography (SE-UPLC).

32. The stable liquid pharmaceutical formulation of claim 31, wherein the formulation comprises no more than 2.5% high molecular weight (HMW) species following agitation by vortexing for up to 120 minutes at room temperature, as determined by SE-UPLC.

33. The stable liquid pharmaceutical formulation of any one of claims 1-30, wherein the formulation comprises no more than 8% high molecular weight (HMW) species after 30 days of storage at 45ºC, as determined by SE-UPLC.

34. The stable liquid pharmaceutical formulation of any one of claims 1-30, wherein the formulation comprises no more than 9% high molecular weight (HMW) species after 40 days of storage at 45ºC, as determined by SE-UPLC.

35. The stable liquid pharmaceutical formulation of any one of claims 1-30, wherein the formulation comprises no more than 11% high molecular weight (HMW) species after 50 days of storage at 45ºC, as determined by SE-UPLC.

36. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 1000, no more than 500, or no more than 150 particles

having a diameter of ≥10 μm in a volume of 2.25 mL after storage for 6 months at 5ºC, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

37. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 1000, no more than 500, or no more than 150 particles having a diameter of ≥10 μm in a volume of 2.25 mL after storage for 36 months at 5ºC, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

38. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 500, no more than 250, or no more than 50 particles having a diameter of ≥25 μm in a volume of 2.25 mL after storage for 6 months at 5ºC, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

39. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 500, no more than 250, or no more than 50 particles having a diameter of ≥25 μm in a volume of 2.25 mL after storage for 6 months at 5ºC, as determined by microscopy, and wherein the formulation contains a phospholipase protein.

40. The stable liquid pharmaceutical formulation of any one of claims 36-39, wherein the phospholipase protein is phospholipase B-like 2 protein.

41. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C, as determined by SE-UPLC.

42. The stable liquid pharmaceutical formulation of any one of claims 1-35, wherein the formulation comprises no more than 4% high molecular weight (HMW) species following agitation for 24 hours at 25°C and storage at (i) 5°C for 6, 12, or 18 months, or (ii) 25°C for 6 months, as determined by SE-UPLC.

43. The stable liquid pharmaceutical formulation of any one of claims 1-42 contained in a glass vial.

44. The stable liquid pharmaceutical formulation of any one of claims 1-42 contained in a syringe.

45. The stable liquid pharmaceutical formulation of claim 44, wherein the syringe comprises a fluorocarbon-coated plunger.

46. The stable liquid pharmaceutical formulation of claim 44, wherein the syringe is a low tungsten syringe.

47. The stable liquid pharmaceutical formulation of any one of claims 44 to 46 that is a prefilled syringe.

48. The stable liquid pharmaceutical formulation of claim 47 that is a prefilled staked needle syringe.

49. The stable liquid pharmaceutical formulation of any one of claims 1-42 contained in a large volume device or bolus injector.

50. A pen or autoinjector delivery device containing a stable liquid pharmaceutical formulation of any one of claims 1-42.

51. The delivery device of claim 50 that is a disposable pen delivery device.

52. The delivery device of claim 50 that is a reusable pen delivery device.

53. A container containing a stable liquid pharmaceutical formulation of any one of claims 1-42.

54. A kit comprising (i) a container containing the stable liquid pharmaceutical formulation of any one of claims 1-42, and (ii) labeling for use of the pharmaceutical formulation.

55. The kit of claim 54, wherein the labeling recites subcutaneous administration of the pharmaceutical formulation.

56. The kit of claim 54, wherein the labeling recites intravenous administration of the pharmaceutical formulation.

57. A unit dosage form comprising a stable liquid pharmaceutical formulation of any one of claims 1-42, wherein the antibody is present in an amount of from 1 mg to 500 mg.

58. The unit dosage form of claim 57, wherein the antibody is present in an amount of about 300 mg.

59. The unit dosage form of claim 57, wherein the antibody is present in an amount of about 200 mg.

60. The unit dosage form of claim 57, wherein the antibody is present in an amount of about 100 mg.

61. The unit dosage form of any one of claims 57-60, wherein the formulation is contained in a syringe.

62. The unit dosage form of claim 61, wherein the syringe is a prefilled syringe.

63. A safety system delivery device containing a stable liquid pharmaceutical formulation of any one of claims 1-42.

64. The safety system delivery device of claim 63, including a safety sleeve configured to extend by manual operation.

65. The safety system delivery device of claim 63, including a safety sleeve configured to automatically extend following injection of the stable liquid pharmaceutical formulation.

(≥10µm) #/Container by microscopic method

5°C, Months	PEG 3350 Conc. (w/v)			Poloxamer 188 Conc. (w/v)		
	0.02%	0.04%	0.1%	0.02%	0.04%	0.1%
6	15	38	99	36	34	84
12	23	61	36	42	25	34
18	25	42	38	86	40	114
24	61	103	57	91	105	143
36	25	17	38	32	19	67

(≥25µm) #/Container by microscopic method

5°C, Months	PEG 3350 Conc. (w/v)			Poloxamer 188 Conc. (w/v)		
	0.02%	0.04%	0.1%	0.02%	0.04%	0.1%
6	0	11	42	17	2	19
12	6	19	11	17	8	4
18	8	6	11	21	4	30
24	8	13	11	11	15	15
36	15	0	6	2	4	17

FIG. 1

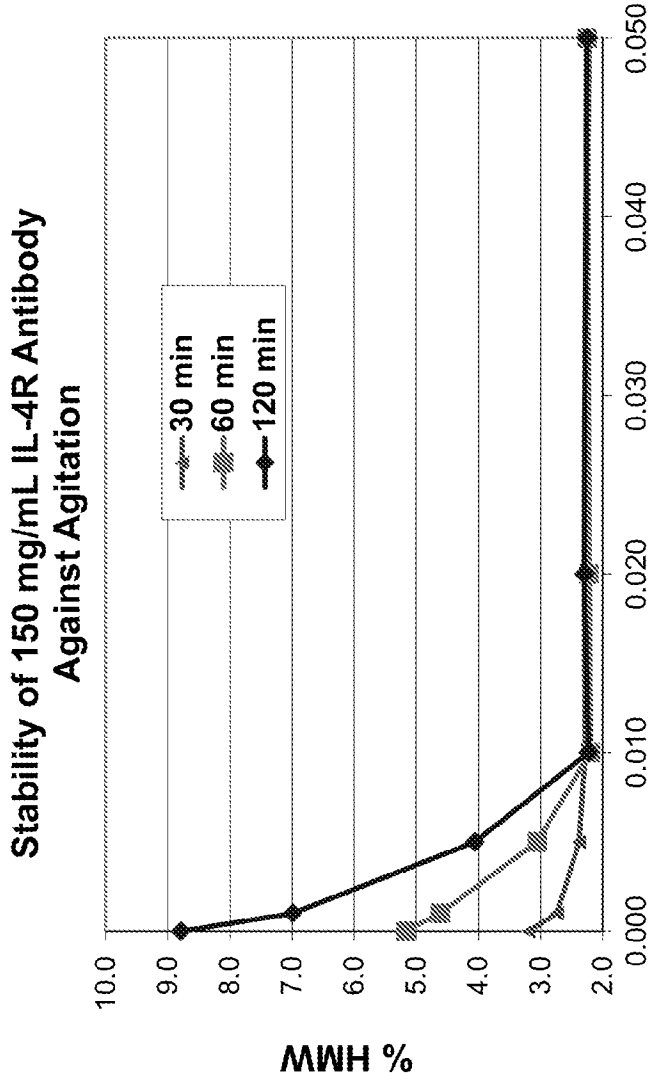

Stability of 150 mg/mL IL-4R Antibody Against Agitation
30 min
60 min
120 min
MWH %
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
0.000
0.010
0.020
0.030
0.040
0.050
PEG3350 Concentration (% w/v)

FIG. 2A

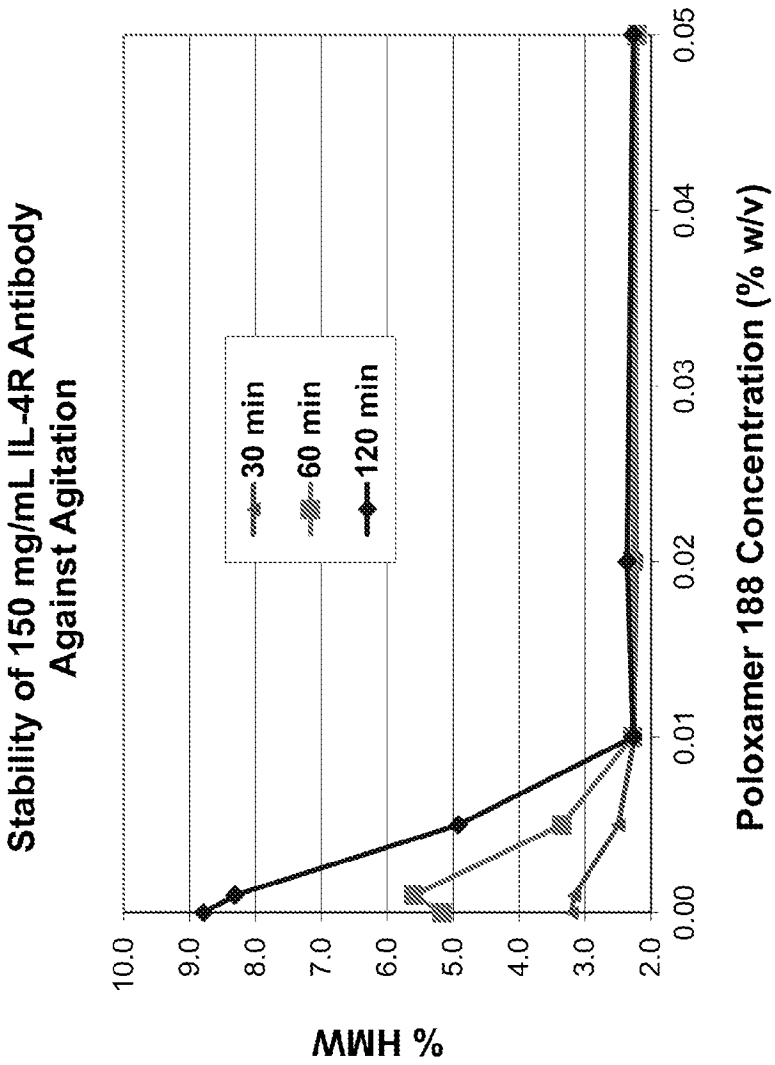

Stability of 150 mg/mL IL-4R Antibody
Against Agitation
30 min
60 min
120 min
MWH %
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
0.00
0.01
0.02
0.03
0.04
0.05
Poloxamer 188 Concentration (% w/v)

FIG. 2B

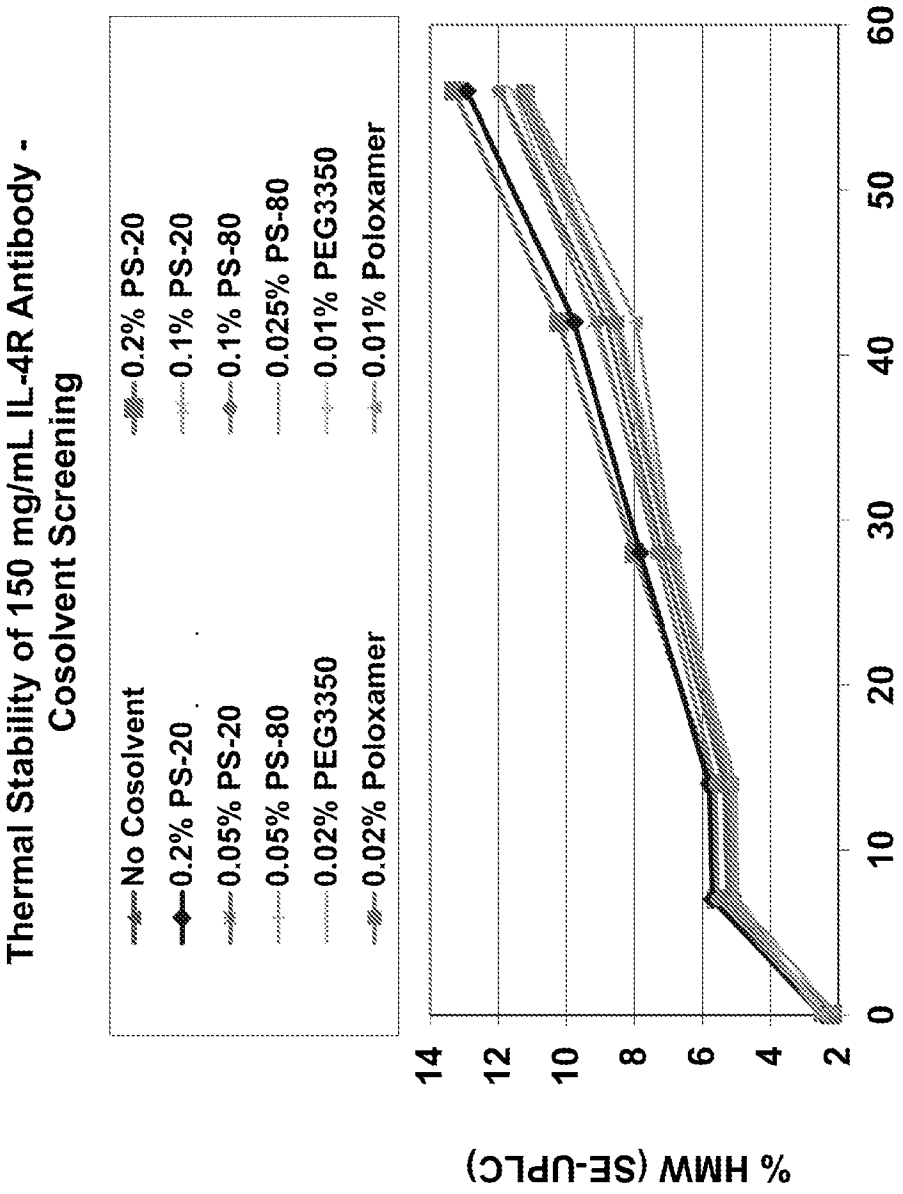

Thermal Stability of 150 mg/mL IL-4R Antibody - Cosolvent Screening
No Cosolvent
0.2% PS-20
0.2% PS-20
0.1% PS-20
0.05% PS-20
0.1% PS-80
0.05% PS-80
0.025% PS-80
0.02% PEG3350
0.01% PEG3350
0.02% Poloxamer
0.01% Poloxamer
% HMW (SE-UPLC)
14
12
10
8
6
4
2
0
10
20
30
40
50
60
Incubation Time at 45°C (days)

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/020660

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K39/00 A61K47/10 A61K47/34
ADD. A61K47/18 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/047954 A1 (REGENERON PHARMA [US]; DIX DANIEL B [US]; TANG XIAOLIN [US]) 12 April 2012 (2012-04-12)	1-26, 30-65
Y	page 25, line 1415; examples 1, 6; table 2	27-29
Y	WO 2013/131866 A1 (HOFFMANN LA ROCHE [CH]; GOLDBACH PIERRE [FR] ET AL.) 12 September 2013 (2013-09-12) formulation F16; claim 1	27-29
Y	WO 2015/159254 A1 (BIOCON LTD [IN]; MYLAN GMBH [CH]) 22 October 2015 (2015-10-22) claim 1; table 2B	27-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2023	01/08/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frelichowska, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2023/020660

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/020660

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/020660

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