STABLE ANTIBODY FORMULATION

RELATED APPLICATIONS

[001] This application claims priority under 35 U.S.C. 119(e) to U.S. Provisional Application Serial No. 63/637,673 entitled "Stable Antibody Formulation", filed April 23, 2024, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD

[002] The present disclosure relates to the field of therapeutic antibody formulations. More specifically, the present disclosure relates to the field of pharmaceutical formulations comprising a human antibody that specifically binds to human lymphocyte activation gene-3 (LAG-3) protein and a human antibody that specifically binds to human Program death-1 (PD-1) receptor.

SEQUENCE LISTING

[003] An official copy of the sequence listing is submitted concurrently with the specification via Patent Center. The contents of electronic sequence listing (11730WO01_Sequence_Listing_ST26.xml; Size: 20,480 bytes; and Date of Creation: April 18, 2025) is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND

[004] Programmed death-1 (PD-1) receptor signaling in the tumor microenvironment plays a key role in allowing tumor cells to escape immune surveillance by the host immune system. The PD-1 receptor has two ligands, PD-ligand-1 (PD-L1) and PD-L2. Blockade of the PD-1 signaling pathway has demonstrated clinical activity in patients with multiple tumor types, and antibody therapeutics that block PD-1/PDL1 signaling (e.g., nivolumab, pembrolizumab, atezolizumab, durvalumab, and cemiplimab) have been approved for the treatment of various cancers including, for example, metastatic melanoma and metastatic squamous non-small cell lung cancer.

[005] Like PD-1, lymphocyte activation gene-3 (LAG-3) negatively regulates T-cell activity. LAG-3 (also called CD223) is a 503 amino acid transmembrane protein receptor expressed on activated CD4 and CD8 T cells, γδ T cells, natural killer T cells, B-cells, natural killer cells, plasmacytoid dendritic cells and regulatory T cells. LAG-3 is a

member of the immunoglobulin (Ig) superfamily. The primary function of LAG-3 is to attenuate the immune response. LAG-3 binding to MHC class II molecules results in delivery of a negative signal to LAG-3-expressing cells and down-regulates antigen-dependent CD4 and CD8 T cell responses. LAG-3 negatively regulates the ability of T cells to proliferate, produce cytokines and lyse target cells, termed as 'exhaustion' of T cells. LAG-3 is also reported to play a role in enhancing T regulatory (Treg) cell function (Pardoll 2012, Nature Reviews Cancer 12: 252-264).

[006] Since both PD-1 and LAG-3 play important roles in tumor immunity, they are ideal targets for immunotherapy. Targeting both LAG-3 and PD-1 (including in anti-PD-1 resistant tumors) may result in objective responses in patients across several tumor types. However, separately administering two therapeutics can be burdensome to patients and an inefficient use of personnel and supplies in the treatment clinic.

[007] Therapeutic antibodies like anti-LAG3 antibodies and anti-PD-1 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 and subsequent use. For example, therapeutic antibodies in liquid solution are prone to degradation, aggregation, 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. Furthermore, other considerations aside from stability must be taken into account when preparing a liquid antibody formulation. Examples of such additional considerations include the viscosity of the solution and the concentration of antibody that can be accommodated by a given formulation, and the visual quality or appeal of the formulation. Thus, when formulating a therapeutic antibody, great care must be taken to arrive at a formulation that remains stable, contains an adequate concentration of antibody, and possesses a suitable viscosity as well as other properties which enable the formulation to be conveniently administered to patients.

[008] Antibody co-formulations require particular consideration as antibodies have different properties and require specific excipients and amounts to maintain stability. For example, the two or more antibodies can exhibit different tolerances to stress conditions and co-formulated antibodies can form impurities including heterodimers.

[009] While anti-LAG-3 antibodies and anti-PD-1 antibodies are known, there remains a need in the art for novel co-formulations comprising both antibodies that are sufficiently stable and suitable for administration to patients.

BRIEF SUMMARY

[010] The present disclosure satisfies the aforementioned need by providing stable pharmaceutical formulations comprising a human antibody that specifically binds to human lymphocyte activation gene-3 (LAG-3) and a human antibody that specifically binds to programmed death 1 (PD-1).

[011] In one aspect, a stable pharmaceutical formulation is provided, wherein the formulation comprises:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) a buffer,

(d) a sugar,

(e) a non-ionic surfactant, and

(f) an amino acid, at pH 6.0 ± 0.3

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

[012] In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from 20 mg/ml to 60 mg/ml, or from 35 mg/ml to 52 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 40 mg/ml ± 10 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 47.1 mg/ml ± 5 mg/ml.

[013] In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from 5 mg/ml to 50 mg/ml, or from 9 mg/ml to 40 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 10.3 mg/ml ± 1 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 35 mg/ml ± 3.5 mg/ml.

[014] In some embodiments, the buffer can be phosphate buffer, acetate buffer, or histidine buffer. In some aspects, the buffer is phosphate buffer. In some aspects, the buffer is acetate buffer. In some aspects, the buffer is histidine buffer. The buffer concentration can range from about 5 mM to about 20 mM. In some aspects, the buffer concentration is 10 mM ± 2 mM.

[015] In some embodiments, sugar is present in the pharmaceutical formulation at a concentration of from about 5% to about 12% w/v, or at a concentration of about 9% ± 2% w/v. In some aspects, the sugar is sucrose.

[016] In some embodiments, the stable pharmaceutical formulation comprises a non-ionic surfactant, for example, polysorbate. In some aspects, the non-ionic surfactant is present at a concentration of from 0.08% to 0.22% w/v. In some aspects, the non-ionic surfactant is present at a concentration of 0.1% ± 0.025% w/v. In some aspects, the non-ionic surfactant is polysorbate 80 and is present at a concentration of 0.1% ± 0.025% w/v.

[017] In some embodiments, the stable pharmaceutical formulation comprises an amino acid, for example, arginine or/or proline. In some aspects, the amino acid is arginine. In some aspects, the amino acid is proline. In some aspects, the amino acid is arginine and proline. In some aspects, the arginine is present at a concentration of from 12mM to 23mM. In some aspects, the arginine is present at a concentration of 16mM ± 4mM. In some aspects, the arginine is present at a concentration of 18.8mM ± 4mM. In some aspects, the proline is present at a concentration of from 0.07mM to 0.36mM. In some aspects, the proline is present at a concentration of 0.09mM ± 0.02mM. In some aspects, the proline is present at a concentration of 0.3mM ± 0.06mM.

[018] In some aspects, the stable pharmaceutical formulation as disclosed herein further comprises:

(a) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(c) sucrose at a concentration of no more than about 250 mg/ml,

(d) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(e) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(f) proline at a concentration of no more than about 2 mg/ml, and

(i) water for Injection, USP, at pH 6.0 ± 0.3.

[019] In some aspects, the stable pharmaceutical formulation as disclosed herein further comprises:

(a) the buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.5 mg/ml,

(c) sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml,

(d) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(e) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1 mg/ml, and

(f) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml.

[020] In some aspects, the stable pharmaceutical formulation as disclosed herein further comprises:

(a) the buffer comprising histidine at a concentration of about 0.74 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(c) sucrose at a concentration of about 97 mg/ml,

(d) polysorbate 80 at a concentration of about 1.1 mg/ml,

(e) arginine hydrochloride at a concentration of about 4 mg/ml, and

(f) proline at a concentration of about 0.9 mg/ml.

[021] Provided herein are stable pharmaceutical formulations comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.7% ± 2% w/v sucrose,

(e) 0.11% ± 0.03% w/v polysorbate 80,

(f) 18.8mM ± 4mM arginine, and

(g) 0.09% ± 0.02% w/v proline, at pH 6.0 ± 0.3;

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of

SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

[022] Also provided herein are stable pharmaceutical formulations comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.0% ± 1.8% w/v sucrose,

(e) 0.12% ± 0.03% w/v polysorbate 80,

(f) 16mM ± 4mM arginine, and

(g) 0.3% ± 0.06% w/v proline, at pH 6.0 ± 0.3;

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

[023] Also provided herein is a stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.0% ± 1.8% w/v sucrose,

(e) 0.12% ± 0.03% w/v polysorbate 80,

(f) 16mM ± 4mM arginine, and

(g) 0.3% ± 0.06% w/v or 0.09% ± 0.02% w/v proline, at pH 6.0 ± 0.3;

wherein the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises: three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

[024] In some embodiments, provided herein is a stable pharmaceutical formulation comprising:

a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of an HCVR, and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of an LCVR,

wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8;

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18,

(c) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(e) sucrose at a concentration of no more than about 250 mg/ml,

(f) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(g) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(h) proline at a concentration of no more than about 2 mg/ml, and

(i) water for Injection, USP, at pH 6.0 $\pm$ 0.3,

wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 10 mg/ml to about 100 mg/ml, and the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 5 mg/ml to about 50 mg/ml.

[025] In some aspects, the anti-LAG3 antibody as disclosed herein comprises the HCVR comprising the amino acid sequence of SEQ ID NO: 1 and the LCVR comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the anti-LAG3 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 aspects, the anti-PD-1 antibody as disclosed herein comprises the HCVR comprising the amino acid sequence of SEQ ID NO: 11 and the LCVR comprising the amino acid sequence of SEQ ID NO: 12. In some aspects, the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[026] In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 20 mg/ml to about 75 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 25 mg/ml to about 60 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 35 mg/ml to about 55 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 40 mg/ml to about 50 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of about 47 mg/ml.

[027] In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 8 mg/ml to about 25 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 10 mg/ml to about 15 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of about 10 mg/ml.

[028] In some embodiments, the stable pharmaceutical formulation as described herein comprises:

(c) the buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.5 mg/ml,

(e) sucrose at a concentration of from 50 ± 2.5 mg/ml to 100 ± 20 mg/ml,

(f) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(g) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1 mg/ml, and

(h) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml.

[029] In some embodiments, the stable pharmaceutical formulation as described herein comprises:

(c) the buffer comprising histidine at a concentration of about 0.74 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(e) sucrose at a concentration of about 97 mg/ml,

(f) polysorbate 80 at a concentration of about 1.1 mg/ml,

(g) arginine hydrochloride at a concentration of about 4 mg/ml, and

(h) proline at a concentration of about 0.9 mg/ml.

[030] In some embodiments, provided herein is a stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of an HCVR, and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8;

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18,

(c) a buffer comprising histidine at a concentration of about 0.74 mg/ml,

(d) sucrose at a concentration of about 97 mg/ml,

(e) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(f) arginine hydrochloride at a concentration of about 4 mg/ml,

(g) proline at a concentration of about 0.9 mg/ml,

(h) polysorbate 80 at a concentration of about 1.1 mg/ml; and

(i) water for Injection, USP, at pH 6.0 ± 0.3;

wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of about 47 mg/ml, and the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of about 10 mg/ml.

[031] In some embodiments, the stable pharmaceutical formulations described herein comprise antibodies or antigen-binding fragments thereof that are at least 94% pure when stored at 25°C/60% relative humidity for 1 month. In some embodiments, the stable pharmaceutical formulations described herein comprise antibodies or antigen-binding fragments thereof that exhibit potency of at least about 95% after storage at 5°C for 12 months.

[032] In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 1. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody LCVR that comprises the amino acid sequence of SEQ ID NO: 2. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 1 and LCVR that comprises the amino acid sequence of SEQ ID NO: 2.

[033] In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 11. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody LCVR that comprises the amino acid sequence of SEQ ID NO: 12. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 11 and LCVR that comprises the amino acid sequence of SEQ ID NO: 12.

[034] In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody that comprises a light chain comprising the amino acid sequence of SEQ ID NO: 10. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody that 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.

[035] In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody that comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[036] In some embodiments, a stable pharmaceutical formulation of any of the preceding aspects is provided in a container. In some aspects, the container comprises 1600 mg of the anti-LAG3 antibody. In some aspects, the container comprises 800 mg of the anti-LAG3 antibody. In some aspects, the container comprises 400 mg of the anti-LAG3 antibody. In some aspects, the container comprises 350 mg of the anti-PD-1 antibody. In some aspects, the container comprises 175 mg of the anti-PD-1 antibody. In some aspects, the anti-LAG3 antibody to anti-PD-1 antibody are present in the formulation in a ratio of about 1:0.875. In some aspects, the anti-LAG3 antibody to anti-PD-1 antibody are present in the formulation in a ratio of about 1:0.219.

[037] In one embodiment, the container is a vial, such as a Type 1 clear glass vial or polycarbonate vial. In one embodiment, the vial is 2ml, 5ml, 10 mL, or 20 ml Type 1 clear glass vial. In one embodiment, the vial is 2ml Type 1 clear glass vial. In one embodiment, the vial is 5ml Type 1 clear glass vial. In one embodiment, the vial is 10 mL Type 1 clear glass vial. In one embodiment, the vial is 20 ml Type 1 clear glass vial. In one embodiment, the glass vial is a type 1 borosilicate glass vial with a fluorocarbon-coated butyl rubber stopper. In one embodiment, the container is a microinfuser. In one embodiment, the container is a syringe. In one embodiment, the syringe is low Tungsten glass. In one embodiment, the container is a prefilled syringe. In one embodiment, the syringe comprises a fluorocarbon-coated plunger. In certain embodiments, the syringe is a 1 mL or 2.25 mL long glass syringe containing less than about 500 parts per billion of tungsten equipped with a 27-G needle, a fluorocarbon–coated butyl rubber stopper, and a latex-free, non-cytotoxic rubber tip cap. In one embodiment, the syringe is a 1 mL long glass syringe equipped with a 27-G thin wall needle, a FLUROTEC–coated 4023/50 rubber plunger, and a FM 27 rubber tip cap. In one embodiment, the syringe is a 1 mL, 2

mL, 3 mL, 5 mL, or 10 mL, plastic syringe fitted with a needle. In one embodiment, the container is an autoinjector. In some embodiments, the stable pharmaceutical formulation described herein is contained in an autoinjector. In certain embodiments, the present disclosure provides a prefilled syringe comprising a stable pharmaceutical formulation according to any of the above embodiments. In certain embodiments the present disclosure provides a glass vial comprising a stable pharmaceutical formulation comprising according to any of the above embodiments.

[038] In one aspect, a kit comprising a stable pharmaceutical formulation of any one of the preceding aspects, a container, and instructions is provided. In one embodiment, the container is a glass vial. In one embodiment, the container is a prefilled syringe. In one embodiment, the syringe is a 1 mL or 2.25mL long glass syringe equipped with a 27-G thin wall needle, a FLUROTEC–coated 4023/50 rubber plunger, and a FM 27 rubber tip cap. In one embodiment, the syringe is a 1 mL, 2 mL, 3 mL, 5 mL, or 10 mL plastic syringe fitted with a needle.

[039] Also provided are pharmaceutical formulations as disclosed herein for use in a method of treating cancer or inhibiting the growth of a tumor in a subject in need thereof. In some embodiments, the pharmaceutical formulation is administered intravenously, subcutaneously, or intraperitoneally. In some embodiments, the cancer is selected from the group consisting of astrocytoma, bladder cancer, blood cancer, bone cancer, brain cancer, breast cancer, cervical cancer, clear cell renal cell carcinoma, colorectal cancer, microsatellite-intermediate colorectal cancer, cutaneous squamous cell carcinoma, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, fibrosarcoma, gastric cancer, glioblastoma, glioblastoma multiforme, head and neck squamous cell carcinoma, hepatic cell carcinoma, leukemia, liver cancer, leiomyosarcoma, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, nasopharyngeal cancer, non-small cell lung cancer, osteosarcoma, ovarian cancer, pancreatic cancer, primary and/or recurrent cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, squamous cell cancer, synovial sarcoma, thyroid cancer, triple negative breast cancer, uterine cancer, and Wilms' tumor.

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

BRIEF DESCRIPTION OF THE FIGURES

[041] Figure 1 provides a visual representation of the impact of long-term storage of the various formulation compositions at 2-8°C by measuring the following parameters over time: % HMW (SE-UPLC), % Purity (SE-UPLC), % LMW (SE-UPLC), Δ % Region 1C (iCIEF), Δ % REGN2810 (iCIEF), Δ % Region 2C (iCIEF), Δ % Region 3C (iCIEF), Δ % REGN3767 (iCIEF), Δ % Region 4C (iCIEF), % Purity (NR-MCE), % LMW (NR-MCE), % Heterodimer (LC-MS), ≥10µm Particles/Container (HIAC), and ≥ 25µm Particles/Container (HIAC). Abbreviations: size-exclusion ultra performance liquid chromatography (SE-UPLC), imaged capillary isoelectric focusing (iCIEF), non-reduced microchip capillary electrophoresis (NR-MCE), and liquid chromatography mass spectrometry (LC-MS).

DETAILED DESCRIPTION

[042] Before the present methods are 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.

[043] Standard methods in molecular biology are described Sambrook, Fritsch and Maniatis (1982 & 1989 2nd Edition, 2001 3rd Edition) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Sambrook and Russell (2001) Molecular Cloning, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Wu (1993) Recombinant DNA, Vol. 217, Academic Press, San Diego, Calif.). Standard methods also appear in Ausbel, et al. (2001) Current Protocols in Molecular Biology, Vols. 1-4, John Wiley and Sons, Inc. New York, N.Y., which describes cloning in bacterial cells and DNA mutagenesis (Vol. 1), cloning in mammalian cells and yeast (Vol. 2), glycoconjugates and protein expression (Vol. 3), and bioinformatics (Vol. 4).

[044] 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.). Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

[045] Methods for protein purification including immunoprecipitation, chromatography, electrophoresis, centrifugation, and crystallization are described (Coligan, *et al.* (2000) Current Protocols in Protein Science, Vol. 1, John Wiley and Sons, Inc., New York). Chemical analysis, chemical modification, post-translational modification, production of fusion proteins, glycosylation of proteins are described (see, *e.g.*, Coligan, *et al.* (2000) Current Protocols in Protein Science, Vol. 2, John Wiley and Sons, Inc., New York; Ausubel, *et al.* (2001) Current Protocols in Molecular Biology, Vol. 3, John Wiley and Sons, Inc., NY, NY, pp. 16.0.5-16.22.17; Sigma-Aldrich, Co. (2001) Products for Life Science Research, St. Louis, Mo.; pp. 45-89; Amersham Pharmacia Biotech (2001) BioDirectory, Piscataway, N.J., pp. 384-391). Production, purification, and fragmentation of polyclonal and monoclonal antibodies are described (Coligan, *et al.* (2001) Current Protocols in Immunology, Vol. 1, John Wiley and Sons, Inc., New York; Harlow and Lane (1999) Using Antibodies, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Harlow and Lane, supra). Standard techniques for characterizing ligand/receptor interactions are available (see, *e.g.*, Coligan, *et al.* (2001) Current Protocols in Immunology, Vol. 4, John Wiley, Inc., New York).

[046] Monoclonal, polyclonal, and humanized antibodies can be prepared (see, *e.g.*, Sheperd and Dean (eds.) (2000) Monoclonal Antibodies, Oxford Univ. Press, New York, N.Y.; Kontermann and Dubel (eds.) (2001) Antibody Engineering, Springer-Verlag, New York; Harlow and Lane (1988) Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., pp. 139-243; Carpenter, *et al.* (2000) J. Immunol. 165:6205; He, *et al.* (1998) J. Immunol. 160:1029; Tang *et al.* (1999) J. Biol. Chem. 274:27371-27378; Baca *et al.* (1997) J. Biol. Chem. 272:10678-10684; Chothia *et al.* (1989) Nature 342:877-883; Foote and Winter (1992) J. Mol. Biol. 224:487-499; U.S. Pat. No. 6,329,511).

[047] An alternative to humanization is to use human antibody libraries displayed on phage or human antibody libraries in transgenic mice (Vaughan *et al.* (1996) Nature Biotechnol. 14:309-314; Barbas (1995) Nature Medicine 1:837-839; Mendez *et al.* (1997) Nature Genetics 15:146-156; Hoogenboom and Chames (2000) Immunol. Today 21:371-377; Barbas *et al.* (2001) Phage Display: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Kay *et al.* (1996) Phage Display of Peptides and Proteins: A Laboratory Manual, Academic Press, San Diego, Calif.; de Bruin *et al.* (1999) Nature Biotechnol. 17:397-399). Single chain antibodies and diabodies are described (see, *e.g.*, Malecki *et al.* (2002) Proc. Natl. Acad. Sci. USA 99:213-218; Conrath *et al.* (2001) J. Biol. Chem. 276:7346-7350; Desmyter *et al.* (2001) J. Biol. Chem. 276:26285-26290; Hudson and Kortt (1999) J. Immunol. Methods 231:177-189; and U.S. Pat. No. 4,946,778). Bifunctional antibodies are provided (see, *e.g.*, Mack, *et al.* (1995) Proc. Natl. Acad. Sci. USA 92:7021-7025; Carter (2001) J. Immunol. Methods 248:7-15; Volkel, *et al.* (2001) Protein Engineering 14:815-823; Segal, *et al.* (2001) J. Immunol. Methods 248:1-6; Brennan, *et al.* (1985) Science 229:81-83; Raso, *et al.* (1997) J. Biol. Chem. 272:27623; Morrison (1985) Science 229:1202-1207; Traunecker, *et al.* (1991) EMBO J. 10:3655-3659; and U.S. Pat. Nos. 5,932,448, 5,532,210, and 6,129,914). Fully human antibodies may also be developed in genetically engineered mice such as the VelociMouse. See e.g., DeChiara *et al.*, Producing fully ES cell-derived mice from eight-cell stage embryo injections, Methods Enzymol, 476:285-94 (2010); Dechiara *et al.*, VelociMouse: fully ES cell-derived F0-generation mice obtained from the injection of ES cells into eight-cell-stage embryos. Methods Mol Biol, 530:311-24 (2009); U.S. patent nos. 7576259; 7659442; or 7294754, and US2008/0078000A1.

[048] Purification of antigen is not typically necessary for the generation of antibodies. Animals can be immunized with cells bearing the antigen of interest. Splenocytes can then be isolated from the immunized animals, and the splenocytes can fused with a myeloma cell line to produce a hybridoma (see, *e.g.*, Meyaard *et al.* (1997) Immunity 7:283-290; Wright *et al.* (2000) Immunity 13:233-242; Preston *et al.*, supra; Kaithamana *et al.* (1999) J. Immunol. 163:5157-5164).

[049] Antibodies can be conjugated, *e.g.*, to small drug molecules, enzymes, liposomes, polyethylene glycol (PEG). Antibodies are useful for therapeutic, diagnostic, kit or other purposes, and include antibodies coupled, *e.g.*, to dyes, radioisotopes, enzymes, or

metals, *e.g.*, colloidal gold (see, *e.g.*, Le Doussal *et al.* (1991) J. Immunol. 146:169-175; Gibellini *et al.* (1998) J. Immunol. 160:3891-3898; Hsing and Bishop (1999) J. Immunol. 162:2804-2811; Everts *et al.* (2002) J. Immunol. 168:883-889).

[050] Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, *e.g.*, Owens, *et al.* (1994) Flow Cytometry Principles for Clinical Laboratory Practice, John Wiley and Sons, Hoboken, N.J.; Givan (2001) Flow Cytometry, 2nd ed.; Wiley-Liss, Hoboken, N.J.; Shapiro (2003) Practical Flow Cytometry, John Wiley and Sons, Hoboken, N.J.). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, *e.g.*, as diagnostic reagents, are available (Molecular Probes (2003) Catalogue, Molecular Probes, Inc., Eugene, Oreg.; Sigma-Aldrich (2003) Catalogue, St. Louis, Mo.).

[051] Standard methods of histology of the immune system are described (see, *e.g.*, Muller-Harmelink (ed.) (1986) Human Thymus: Histopathology and Pathology, Springer Verlag, New York, N.Y.; Hiatt, *et al.* (2000) Color Atlas of Histology, Lippincott, Williams, and Wilkins, Phila, Pa.; Louis, *et al.* (2002) Basic Histology: Text and Atlas, McGraw-Hill, New York, N.Y.).

[052] Software packages and databases for determining, *e.g.*, antigenic fragments, leader sequences, protein folding, functional domains, glycosylation sites, and sequence alignments, are available (see, *e.g.*, GenBank, Vector NTI® Suite (Informax, Inc, Bethesda, Md.); GCG Wisconsin Package (Accelrys, Inc., San Diego, Calif.); DeCypher® (TimeLogic Corp., Crystal Bay, Nev.); Menne, *et al.* (2000) Bioinformatics 16: 741-742; Menne, *et al.* (2000) Bioinformatics Applications Note 16:741-742; Wren, *et al.* (2002) Comput. Methods Programs Biomed. 68:177-181; von Heijne (1983) Eur. J. Biochem. 133:17-21; von Heijne (1986) Nucleic Acids Res. 14:4683-4690).

[053] 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 V_H) 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 V_L) and a light chain constant region. The light chain constant region comprises one domain (CL1). The V_H and V_L 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 V_H and V_L 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.

[054] Unless specifically indicated otherwise, the term "antibody", as used herein, shall be understood to encompass complete antibody molecules as well as antigen-binding fragments thereof. The term "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to human LAG-3 or an epitope thereof.

[055] 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 human LAG-3 is substantially free of antibodies that specifically bind antigens other than human LAG-3).

[056] 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 $1x10^{-8}$ 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 a given antigen, however, have cross-reactivity to other antigens, such as molecules from other species (orthologs). In the context of the present disclosure, multispecific (*e.g.*, bispecific) antibodies that bind to human LAG-3 as well as one or more additional antigens are deemed to "specifically bind" human LAG-3. In the context of the present disclosure, multispecific (*e.g.*, bispecific) antibodies that bind to human PD-1 as well as one or more additional antigens are deemed to "specifically bind" human PD-1. Moreover, an isolated antibody may be substantially free of other cellular material or chemicals.

[057] Sequence identity may be measured by any method known in the art (*e.g.*, GAP, BESTFIT, and BLAST).

[058] As used herein, the expression "pharmaceutical formulation" means a combination of at least one active ingredient (*e.g.*, a small molecule, macromolecule, compound, 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 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 an anti-LAG3 antibody, or antigen-binding fragment thereof, and an anti-PD-1 antibody, or antigen-binding fragment thereof. More specifically, the present disclosure includes pharmaceutical formulations that comprise:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) a buffer,

(d) a sugar,

(e) a non-ionic surfactant, and

(f) an amino acid, at pH 6.0 ± 0.3

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs

(LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

[059] Specific exemplary components and formulations included within the present invention are described in detail below.

ANTIBODIES THAT BIND SPECIFICALLY TO LAG-3

[060] The pharmaceutical formulations of the present disclosure may comprise a human antibody, or an antigen-binding fragment thereof, that binds specifically to human LAG-3. As used herein, the term "LAG-3" means human lymphocyte activation gene-3. Antibodies to human LAG-3 are described in, for example, U.S. 20100233183, U.S. 20110150892, U.S. 20140286935, WO2015200119, U.S. 20160222116, U.S. 20170022273, U.S. 20170097333, U.S. 20170137517, U.S. 20170267759, U.S. 20170290914, U.S. 20170334995, WO2017062888, WO2016126858, WO2016200782, WO2017087589, WO2017087901, WO2017106129, WO2017149143, WO2017198741, WO2017219995, and WO2017220569.

[061] Exemplary anti-human LAG-3 antibodies that may be included in the pharmaceutical formulations of the present disclosure are set forth in patent application publications U.S. 20170101472 and WO2017062888, the disclosures of which are incorporated by reference in their entirety.

[062] According to certain embodiments of the present disclosure, the anti-human LAG-3 antibody, or antigen-binding fragment thereof, comprises a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 3, an HCDR2 of SEQ ID NO: 4, and an HCDR3 of SEQ ID NO: 5. In certain embodiments, the anti-human LAG-3 antibody, or antigen-binding fragment thereof, comprises an HCVR of SEQ ID NO: 1.

[063] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises a light chain complementary determining region (LCDR) 1 of SEQ ID NO: 6, an LCDR2 of SEQ ID NO: 7, and an

LCDR3 of SEQ ID NO: 8. In certain embodiments, the anti-human LAG-3 antibody, or antigen-binding fragment thereof, comprises an LCVR of SEQ ID NO: 2.

[064] The present disclosure includes formulations comprising anti-LAG-3 antibodies, wherein the anti-LAG-3 antibodies comprise variants of any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein having one or more conservative amino acid substitutions. For example, the present disclosure includes formulations comprising anti-LAG-3 antibodies having HCVR, LCVR and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein.

[065] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises an HCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 1.

[066] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises an LCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 2.

[067] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 1 having no more than 5 amino acid substitutions.

[068] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises an LCVR comprising an amino acid sequence of SEQ ID NO: 2 having no more than 2 amino acid substitutions.

[069] In certain embodiments, the anti-LAG-3 antibody comprises a Fc region elected from the group consisting of human IgG1, IgG2, IgG3, and IgG4 isotypes.

[070] The non-limiting, exemplary antibody used in the Examples herein is referred to as "mAb1". This antibody is also referred to in U.S. 20170101472 as H4sH15482P, and is also known as “REGN3767” or “Fianlimab”. mAb1 (H4sH15482P) comprises an HCVR/LCVR amino acid sequence pair having SEQ ID NOs: 1/2, and HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3 domains represented by SEQ ID NOs: 3 – 4 – 5 / SEQ ID NOs: 6 – 7 – 8.

[071] According to certain embodiments of the present disclosure, the anti-human LAG-3, or antigen-binding fragment thereof, comprises a heavy chain of SEQ ID NO: 9 and a light chain of SEQ ID NO: 10.

[072] It is well known in the art that terminal cleavage of amino acids can occur during production of antibodies (see, for example, Wang *et al* 2007, J. Pharma. Sci. 96: 1-26). Accordingly, in certain embodiments, the anti-LAG-3 antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 9, wherein the C-terminal lysine is absent from the amino acid sequence of SEQ ID NO: 9. In certain embodiments, formulations of the present disclosure contain about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or more of the anti-LAG-3 antibody wherein the C-terminal lysine is absent.

ANTIBODIES THAT BIND SPECIFICALLY TO PD-1

[073] The pharmaceutical formulations of the present disclosure may comprise a human antibody, or an antigen-binding fragment thereof, that binds specifically to PD-1. The term "PD-1" refers to the programmed death-1 protein, a T-cell co-inhibitor, also known as CD279. Antibodies to PD-1 are described in, for example, U.S. 9,987,500, the disclosure of which is incorporated by reference in its entirety.

[074] According to certain embodiments of the present disclosure, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 13, an HCDR2 of SEQ ID NO: 14, and an HCDR3 of SEQ ID NO: 15. In certain embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises an HCVR of SEQ ID NO: 11.

[075] According to certain embodiments of the present disclosure, the anti-PD-1, or antigen-binding fragment thereof, comprises a light chain complementary determining region (LCDR) 1 of SEQ ID NO: 16, an LCDR2 of SEQ ID NO: 17, and an LCDR3 of SEQ ID NO: 18. In certain embodiments, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises an LCVR of SEQ ID NO: 12.

[076] The present disclosure includes formulations comprising anti-PD-1 antibodies, wherein the anti-PD-1 antibodies comprise variants of any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein having one or more conservative amino acid substitutions. For example, the present disclosure includes formulations comprising anti-PD-1 antibodies having HCVR, LCVR and/or CDR amino acid sequences with, e.g.,

10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR and/or CDR amino acid sequences disclosed herein.

[077] According to certain embodiments of the present disclosure, the anti-PD-1, or antigen-binding fragment thereof, comprises an HCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 11.

[078] According to certain embodiments of the present disclosure, the anti-human PD-1, or antigen-binding fragment thereof, comprises an LCVR having 90%, 95%, 98% or 99% sequence identity to SEQ ID NO: 12.

[079] According to certain embodiments of the present disclosure, the anti-human PD-1, or antigen-binding fragment thereof, comprises an HCVR comprising an amino acid sequence of SEQ ID NO: 11 having no more than 5 amino acid substitutions.

[080] According to certain embodiments of the present disclosure, the anti-human PD-1, or antigen-binding fragment thereof, comprises an LCVR comprising an amino acid sequence of SEQ ID NO: 12 having no more than 2 amino acid substitutions.

[081] In certain embodiments, the anti-PD-1 antibody comprises a Fc region elected from the group consisting of human IgG1, IgG2, IgG3, and IgG4 isotypes.

[082] The non-limiting, exemplary antibody used in the Examples herein is referred to as "mAb2". An exemplary antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 11 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 12 is the fully human anti-PD-1 antibody known as REGN2810 (cemiplimab; LIBTAYO®).

[083] According to certain embodiments of the present disclosure, the anti-PD-1 antibody, or antigen-binding fragment thereof, comprises a heavy chain of SEQ ID NO: 19 and a light chain of SEQ ID NO: 20.

[084] It is well known in the art that terminal cleavage of amino acids can occur during production of antibodies (see, for example, Wang *et al* 2007, J. Pharma. Sci. 96: 1-26). Accordingly, in certain embodiments, the anti-PD-1 antibody comprises a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 19, wherein the C-terminal lysine is absent from the amino acid sequence of SEQ ID NO: 19. In certain embodiments, formulations of the present disclosure contain about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98% or more of the anti-PD-1 antibody wherein the C-terminal lysine is absent.

EXCIPIENTS AND pH

[085] 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.

[086] In certain embodiments, the pharmaceutical formulation of the invention comprises at least one organic cosolvent in a type and in an amount that stabilizes both antibodies under conditions of rough handling or agitation, such as, *e.g.,* vortexing. In some embodiments, what is meant by "stabilizes" is the prevention of the formation of more than 3% aggregated antibody of the total amount of antibody (on a molar basis) over the course of rough handling. In some embodiments, rough handling is vortexing a solution containing the antibody and the organic cosolvent for about 60 minutes or about 120 minutes.

[087] In certain embodiments, the organic cosolvent is a non-ionic surfactant, such as an alkyl poly(ethylene oxide). Specific non-ionic surfactants that can be included in the formulations of the present disclosure include, *e.g.*, polysorbates such as polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81, and polysorbate 85; poloxamers such as poloxamer 181, poloxamer 188, poloxamer 407; or polyethylene glycol (PEG). Polysorbate 20 is also known as TWEEN 20, sorbitan monolaurate and polyoxyethylenesorbitan monolaurate. Poloxamer 188 is also known as PLURONIC F68. In some embodiments, the non-ionic surfactant is polysorbate 80.

[088] The amount of non-ionic 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 0.01% ± 0.005% to 0.5% ± 0.25% surfactant. For example, the formulations of the present disclosure may comprise about 0.005%; 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%; about 0.19%; about 0.20%; about 0.21%; about 0.22%; about 0.23%; about 0.24%; about 0.25%; about 0.26%; about

0.27%; about 0.28%; about 0.29%; about 0.30%; about 0.35%; about 0.40%; about 0.45%; about 0.46%; about 0.47%; about 0.48%; about 0.49%; about 0.50%; about 0.55%; or about 0.60% polysorbate 20 or polysorbate 80. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of no more than about 10 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of no more than about 5 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of about 0.25 mg/ml, about 0.5 mg/ml, about 0.75 mg/ml, about 1 mg/ml, about 1.25 mg/ml, about 1.5 mg/ml, about 1.75 mg/ml, about 2 mg/ml, about 2.25 mg/ml, about 2.5 mg/ml, about 2.75 mg/ml, about 3 mg/ml, about 3.25 mg/ml, about 3.5 mg/ml, about 3.75 mg/ml, about 4 mg/ml, about 4.25 mg/ml, about 4.5 mg/ml, about 4.75 mg/ml, about 5 mg/ml, about 5.5 mg/ml, about 6 mg/ml, about 6.5 mg/ml, about 7 mg/ml, about 7.5 mg/ml, about 8 mg/ml, about 8.5 mg/ml, about 9 mg/ml, about 9.5 mg/ml, or about 10 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 9 ± 2.5 mg/ml, from 1 ± 0.25 mg/ml to 8 ± 2 mg/ml, from 1 ± 0.25 mg/ml to 7 ± 2 mg/ml, from 1 ± 0.25 mg/ml to 6 ± 1.5 mg/ml, from 1 ± 0.25 mg/ml to 5 ± 1.5 mg/ml, from 1 ± 0.25 mg/ml to 4 ± 1 mg/ml, from 1 ± 0.25 mg/ml to 3 ± 0.8 mg/ml, or from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise polysorbate 80 at a concentration of about 1.1 mg/ml.

[089] The pharmaceutical formulations of the present disclosure may also comprise one or more stabilizers in a type and in an amount that stabilizes the antibodies under conditions of thermal stress. In some embodiments, what is meant by “stabilizes” is maintaining less than about 0.18% heterodimer formation when the solution containing the two antibodies are stored for 18 months or 24 months at 5°C. In some embodiments, what is meant by “stabilizes” is wherein the formulation containing the antibodies has at least about 99.0% purity when the solution containing the antibodies is kept at about 25°C/60% RH up to 6 months or has at least about 96.0% purity when the solution containing the antibodies is kept at about 45°C/75% RH up to 3 months. As used herein,

"purity" means the major form, i.e., native form, of the antibody by size exclusion, which is generally an intact monomer of the antibody. The term "native" also refers to non-aggregated and non-degraded form of the antibody.

[090] In certain embodiments, the thermal stabilizer is a sugar such as sucrose, the amount of which contained within the formulation can vary depending on the specific circumstances and intended purposes for which the formulation is used. In certain embodiments, the formulations may contain about 1% to about 15% sugar; about 2% to about 14% sugar; about 3% to about 13% sugar; about 4% to about 12% sugar; about 5% to about 12% sugar; about 6% to about 11% sugar; about 7% to about 10% sugar; about 8% to about 11% sugar; or about 9% to about 11% sugar. For example, the pharmaceutical formulations of the present disclosure may comprise 4%± 0.8%; 5% ± 1%; 6% ± 1.2%; 7% ± 1.4%; 8% ± 1.6%; 9% ± 1.8%; 9.7%± 2%; 10% ± 2%; 11% ± 2.2%; 12% ± 2.4%; 13% ± 2.6%; about 14% ± 2.8% sugar; or about 15% ± 3.0% sugar (*e.g.,* sucrose). In certain embodiments, the pharmaceutical formulations of the present disclosure comprise sucrose at a concentration of no more than about 250 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise sucrose at a concentration of from about 10 mg/ml to about 150 mg/ml, from about 20 mg/ml to about 140 mg/ml, from about 25 mg/ml to about 135 mg/ml, from about 30 mg/ml to about 130 mg/ml, from about 35 mg/ml to about 125 mg/ml, from about 40 mg/ml to about 120 mg/ml, from about 45 mg/ml to about 115 mg/ml, or from about 50 mg/ml to about 110 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise sucrose at a concentration of 95 mg/ml, 96 mg/ml, 97 mg/ml, 98 mg/ml, 99 mg/ml, or 100 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise sucrose at a concentration of 97 mg/ml. 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 two antibodies. The term "buffer" as used herein denotes a pharmaceutically acceptable buffer which maintains a stable pH or resists changes in pH of the solution. In preferred embodiments, the buffer comprises histidine. In the context of this disclosure, "histidine buffer" or "buffer comprising histidine" is a buffer comprising the amino acid histidine.

Examples of histidine buffers include histidine chloride, histidine acetate, histidine phosphate, and histidine sulfate. In a one embodiment, the histidine buffer is prepared by dissolving L-histidine and L-histidine hydrochloride (*e.g.,* as monohydrate) in a defined amount and ratio. In one embodiment, the histidine buffer is prepared by titrating L-histidine (free base, solid) with diluted hydrochloric acid. The term "histidine" is used interchangeably with "histidine buffer" throughout this disclosure. In some embodiments, what is meant by "stabilizes" is wherein less than about 1.0% ± 0.05% of the antibody is aggregated (high molecular weight via SE-UPLC) when the solution containing the antibodies and the buffer is kept at about 5°C for up to about 18 months, or up to about 24 months.

[091] In some embodiments, the pharmaceutical formulations of the present disclosure comprise a buffer comprising histidine at a concentration of no more than about 5 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of no more than about 4 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of no more than about 3 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of no more than about 2 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of no more than about 1 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.2 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of 0.7 mg/ml, 0.71 mg/ml, 0.72 mg/ml, 0.73 mg/ml, 0.74 mg/ml, 0.75 mg/ml, 0.76 mg/ml, 0.77 mg/ml, 0.78 mg/ml, 0.79 mg/ml, or 0.8 mg/ml. In some cases, histidine is present in the pharmaceutical formulations at a concentration of 0.74 mg/ml.

[092] In some embodiments, the pharmaceutical formulations of the present disclosure comprise L-histidine hydrochloride monohydrate at a concentration of no more than about 10 mg/ml, no more than about 9 mg/ml, no more than about 8 mg/ml, no more than about 7 mg/ml, no more than 6 about mg/ml, no more than about 5 mg/ml, no more than about 4 mg/ml, no more than about 3 mg/ml, or no more than about 2 mg/ml. In some embodiments, L-histidine hydrochloride monohydrate is present in the pharmaceutical formulations at a concentration of no more than about 5 mg/ml. In some embodiments, L-histidine hydrochloride monohydrate is present in the pharmaceutical formulations at a concentration of no more than about 2 mg/ml. In certain embodiments,

the pharmaceutical formulations of the present disclosure comprise L-histidine hydrochloride monohydrate at a concentration of about 0.25 mg/ml, about 0.5 mg/ml, about 0.75 mg/ml, about 1 mg/ml, about 1.25 mg/ml, about 1.5 mg/ml, about 1.75 mg/ml, about 2 mg/ml, about 2.25 mg/ml, about 2.5 mg/ml, about 2.75 mg/ml, about 3 mg/ml, about 3.25 mg/ml, about 3.5 mg/ml, about 3.75 mg/ml, about 4 mg/ml, about 4.25 mg/ml, about 4.5 mg/ml, about 4.75 mg/ml, about 5 mg/ml, about 5.5 mg/ml, about 6 mg/ml, about 6.5 mg/ml, about 7 mg/ml, about 7.5 mg/ml, about 8 mg/ml, about 8.5 mg/ml, about 9 mg/ml, about 9.5 mg/ml, or about 10 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 9 ± 1.8 mg/ml, from 1 ± 0.2 mg/ml to 8 ± 1.6 mg/ml, from 1 ± 0.2 mg/ml to 7 ± 1.4 mg/ml, from 1 ± 0.2 mg/ml to 6 ± 1.2 mg/ml, from 1 ± 0.2 mg/ml to 5 ± 1.0 mg/ml, from 1 ± 0.2 mg/ml to 4 ± 0.8 mg/ml, from 1 ± 0.2 mg/ml to 3 ± 0.6 mg/ml, or from 1 ± 0.2 mg/ml to 2 ± 0.4 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.5 mg/ml. In certain embodiments, the pharmaceutical formulations of the present disclosure comprise L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml.

[093] In some embodiments, what is meant by "stabilizes" is wherein less than about 2% ± 0.5% or less than about 1% ± 0.5% of the antibody is aggregated (HMW via SE-UPLC) when the solution containing the antibody and the buffer is exposed to 120 minutes of agitation or 4 freeze/thaw cycles. By "native" or "native conformation", what is meant is the antibody fraction that is not aggregated or degraded. This is generally determined by an assay that measures the relative size of the antibody entity, such as a size exclusion chromatographic assay. The non-aggregated and non-degraded antibody elutes at a fraction that equates to the native antibody, and is generally the main elution fraction. Aggregated antibody elutes at a fraction that indicates a size greater than the native antibody (HMW elutes). Degraded antibody elutes at a fraction that indicates a size less than the native antibody (LMW elutes).

[094] In some embodiments, what is meant by "stabilizes" is wherein at least 30% ± 0.5% of the antibody REGN3767 antibody and at least 10% ± 0.5% of the antibody REGN2810 antibody is in its main charge form as determined by cation exchange chromatography

when the solution containing the antibody and the buffer is kept at about 5°C for up to about 24 months. By "main charge" or "main charge form", what is meant is the fraction of antibody that elutes from an ion exchange resin in the main peak, which is generally flanked by more "basic" peaks on one side and more "acidic" peaks on the other side.

[095] The pharmaceutical formulations of the present disclosure may have a pH of from about 5.2 to about 6.4. For example, the formulations of the present disclosure may have a pH of about 5.5; about 5.6; about 5.7; about 5.8; about 5.9; about 6.0; about 6.1; about 6.2; about 6.3; about 6.4; or about 6.5. In some embodiments, the pH is 6.0 ± 0.4; 6.0 ± 0.3; 6.0 ±0.2; 6.0± 0.1; about 6.0; or 6.0.

[096] 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 – 7.4. In certain embodiments, the buffer comprises a histidine buffer. In certain embodiments, the histidine buffer is present at a concentration of 5 mM ± 1 mM to 15 mM ± 3 mM; 6 mM ± 1.2 mM to 14 mM ± 2.8 mM; 7 mM ± 1.4 mM to 13 mM ± 2.6 mM; 8 mM ± 1.6 mM to 12 mM ± 2.4 mM; 9 mM ± 1.8 mM to 11 mM ± 2.2 mM; 10 mM ± 2 mM; or about 10 mM. In certain embodiments, the buffer system comprises histidine at 10 mM ± 2 mM, at a pH of 6.0 ± 0.3. In certain embodiments, the histidine buffer comprises L-histidine and L-histidine monohydrochloride monohydrate. In one embodiment, the histidine buffer comprises L-histidine at a concentration of 5.0 mM ± 1.0 mM. In one embodiment, the histidine buffer comprises L-histidine monohydrochloride monohydrate at a concentration of 5.0 mM ± 1.0 mM. In one embodiment, the histidine buffer comprises L-histidine at a concentration of 5.0 mM ± 1.0 mM and L-histidine monohydrochloride monohydrate at a concentration of 5.0 mM ± 1.0 mM.

[097] The present disclosure includes "buffer-free" or "self-buffering" formulations. In certain embodiments, a formulation is considered "buffer-free" or "self-buffering" if it does not include a separate buffering component. In such embodiments, the active agent/protein component (e.g., antibody or antibody combination) may function as a self-buffering agent, thereby maintaining the pH within a desired range under a variety of storage conditions. The present disclosure thus includes formulations comprising the antibody or combination of antibodies, and one or more of a tonicity agent, a stabilizer, and/or a surfactant, but without an added buffering component.

[098] The pharmaceutical formulations of the present disclosure may also comprise one or more excipients that serve as tonicifiers in formulations containing the anti-PD-1 antibody in combination with the anti-LAG-3 antibody (*e.g.*, 57.4 mg/ml total antibody), and in some aspects, a higher concentration of the two antibodies (*e.g.,* 75 mg/ml total antibody). In certain embodiments, the tonicifier is an amino acid. In one embodiment, the amino acid is arginine hydrochloride. In one embodiment, the pharmaceutical formulation of the present disclosure contains arginine hydrochloride at a concentration of 1 mM, 10 mM, 15 mM, 16 mM, 18.8 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, 50 mM, 55 mM, 60 mM, 65 mM, 70 mM, 75 mM, 80 mM, 85 mM, or 90 mM. In certain embodiments, formulations may contain about 1 mM to about 80 mM; about 10 mM to about 30 mM arginine hydrochloride; or about 20 mM arginine hydrochloride. For example, the pharmaceutical formulations of the present disclosure may comprise 1 mM ± 0.2 mM, 10 mM ± 2 mM, 15 mM ± 3 mM, 16 mM ± 4 mM, 18.8 mM ± 4 mM, 20 mM ± 4 mM, 25 mM ± 5 mM, 30 mM ± 6 mM, 35 mM ± 7 mM, 40 mM ± 8 mM, 45 mM ± 9 mM, 50 mM ± 10 mM, 55 mM ± 11 mM, 60 mM ± 12 mM, 65 mM ± 13 mM, 70 mM ± 14 mM, 75 mM ± 15 mM, 80 mM ± 16 mM, 85 mM ± 17 mM, or 90 mM ± 18 mM arginine hydrochloride.

[099] Herein, a "tonicity modifier" or "tonicifier" refers to a reagent whose inclusion within a formulation increases osmolality and osmolarity of the formulation. In some embodiments, a tonicifier is used to modify a solution to such that the osmotic characteristics are similar to or compatible with physiologic fluids. In certain embodiments, the tonicifier is an amino acid. In one embodiment, the amino acid is arginine hydrochloride. In one embodiment, the pharmaceutical formulation of the present disclosure contains arginine hydrochloride at a concentration of about 15.0 mM to about 22.6 mM, or about 12.8 mM to about 19.2 mM arginine hydrochloride, or about 16 mM ± 4 mM or 18.8 mM ± 4 mM. In some cases, the pharmaceutical formulation of the present disclosure comprises arginine hydrochloride at a concentration of no more than about 10 mg/ml, no more than about 9 mg/ml, no more than about 8 mg/ml, no more than about 7 mg/ml, no more than about 6 mg/ml, or no more than about 5 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises arginine hydrochloride at a concentration of no more than about 5 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises arginine

hydrochloride at a concentration of from 1 ± 0.2 mg/ml to 5 ± 1 mg/ml, from 2 ± 0.4 mg/ml to 5 ± 1 mg/ml or from 3 ± 0.6 mg/ml to 5 ± 1 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises arginine hydrochloride at a concentration of about 3.5 mg/ml, about 3.6 mg/ml, about 3.7 mg/ml, about 3.8 mg/ml, about 3.9 mg/ml, about 4 mg/ml, about 4.1 mg/ml, about 4.2 mg/ml, about 4.3 mg/ml, about 4.4 mg/ml, or about 4.5 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises arginine hydrochloride at a concentration of about 4 mg/ml. In one embodiment, the amino acid is proline. In one embodiment, the pharmaceutical formulation of the present disclosure contains proline in an amount of about 0.07% to about 0.11% w/v proline or about 0.24% to about 0.36% w/v proline, or about 0.3% w/v ± 0.01% w/v proline or 0.09% w/v ± 0.01% w/v proline. In some aspects, the formulation has an osmolality at about 390 mOsm/kg and is suitable for IV administration upon dilution. In some cases, the pharmaceutical formulation of the present disclosure comprises proline at a concentration of no more than about 2 mg/ml, no more than about 1.5 mg/ml, or no more than about 1 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises proline at a concentration of from 0.1 ± 0.1 mg/ml to 0.8 ± 0.2 mg/ml, 0.2 ± 0.1 mg/ml to 0.7 ± 0.25 mg/ml, 0.3 ± 0.1 mg/ml to 0.7 ± 0.25 mg/ml, 0.4 ± 0.1 mg/ml to 0.7 ± 0.25 mg/ml, or 0.5 ± 0.1 mg/ml to 0.7 ± 0.25 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises proline at a concentration of about 0.5 mg/ml, 0.6 mg/ml, 0.7 mg/ml, 0.8 mg/ml, 0.9 mg/ml, or 1 mg/ml. In some cases, the pharmaceutical formulation of the present disclosure comprises proline at a concentration of about 0.9 mg/ml.

[0100] In some embodiments, the pharmaceutical formulation of the present disclosure comprises:

(a) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(c) sucrose at a concentration of no more than about 250 mg/ml,

(d) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(e) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(f) proline at a concentration of no more than about 2 mg/ml, and

(g) water for Injection, USP, at pH 6.0 ± 0.3,

[0101] In some embodiments, the pharmaceutical formulation of the present disclosure comprises:

(a) a buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.2 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.4 mg/ml,

(c) sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml,

(d) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(e) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1 mg/ml, and

(f) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml.

[0102] In some embodiments, the pharmaceutical formulation of the present disclosure comprises:

(a) a buffer comprising histidine at a concentration of about 0.74 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(c) sucrose at a concentration of about 97 mg/ml,

(d) polysorbate 80 at a concentration of about 1.1 mg/ml,

(e) arginine hydrochloride at a concentration of about 4 mg/ml, and

(f) proline at a concentration of about 0.9 mg/ml.

[0103] In one embodiment, the pharmaceutical formulation of the present disclosure contains both arginine hydrochloride and proline in compatible amounts. In some aspects, the formulation comprises about 15.0 mM to about 22.6 mM arginine hydrochloride with proline in an amount of about 0.07% to about 0.11% w/v proline, or 12.8 mM to about 19.2 mM arginine hydrochloride with proline in an amount of about 0.24% to about 0.36% w/v proline, or 18.8 mM ± 4 mM arginine hydrochloride and 0.09% w/v ± 0.02% w/v proline. In some aspects, the formulation comprises 16 mM ± 4 mM arginine hydrochloride and 0.3% w/v ± 0.06% w/v proline.

[0104] During the antibody purification process, it may be desired or necessary to exchange one buffer for another to achieve appropriate excipient concentrations, antibody concentration, pH, etc. Buffer exchange can be accomplished, *e.g.*, by ultrafiltration/diafiltration (UF/DF) using, *e.g.,* a semi-permeable tangential flow filtration membrane. Use of such techniques, however, has the potential to cause the Gibbs-Donnan effect [Bolton et al., 2011, Biotechnol. Prog. 27(1):140-152]. The buildup of

positive charge on the product side of the membrane during protein concentration is counterbalanced electrically by the preferential movement of positive ions to the opposite side of the membrane. The potential consequence of this phenomenon is that the final concentrations of certain components (*e.g.*, arginine hydrochloride, histidine, L-proline, etc.) may be lower than the intended target concentrations of these components due to the electrostatic repulsion of positively charged diafiltration buffer excipients to the positively charged antibody protein during the UF/DF step. Thus, the present disclosure includes formulations in which the concentration of, *e.g.*, histidine and/or arginine hydrochloride vary from the recited amounts or ranges herein due to the Gibbs-Donnan effect.

[0105] Volume exclusion describes the behavior of highly concentrated samples in which a significant portion of the total volume of the solution is taken up by the solute, especially large molecules such as proteins, excluding the solvent from this space. This then decreases the total volume of solvent available for other solutes to be dissolved in, which may result in unequal partition across the ultrafiltration membrane. Thus, the present disclosure includes formulations in which the concentration of, *e.g.*, histidine and/or arginine hydrochloride may vary from the recited amounts or ranges herein due to the volume exclusion effect.

[0106] During the manufacture of the formulations of the present disclosure, variations in the composition of the formulation may occur. These variations may include the concentration of the active ingredient, the concentration of the excipients, and/or the pH of the formulation. Because changes in any of these parameters could potentially impact the stability or potency of the drug product, proven acceptable range (PAR) studies were conducted to assess whether variations in the formulation, within the defined ranges, would impact the stability of the antibody. Accordingly, the present disclosure includes formulations comprising both anti-LAG-3 antibodies and anti-PD-1 antibodies which are stable and retain potency with up to 50% variation in the excipient concentration. For example, included herein are antibody coformulations, wherein stability and potency of said formulations is unaffected by ± 10%, ± 20%, ±30%, ± 40% or ± 50% variation in the concentration of antibody, sucrose, histidine buffer and/or polysorbate.

STABILITY AND OTHER PROPERTIES OF THE PHARMACEUTICAL FORMULATIONS

[0107] The pharmaceutical formulations of the present disclosure typically 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 chemical structure or biological function after storage under defined conditions. A formulation may be stable even though the antibody contained therein does not maintain 100% of its chemical structure or biological function 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 or function after storage for a defined amount of time may be regarded as "stable".

[0108] Stability can be measured, *inter alia*, by determining the percentage of native antibody that remains in the formulation after storage for a defined amount of time at a defined temperature. The percentage of native antibody can be determined by, *inter alia*, size exclusion chromatography (*e.g.*, size exclusion ultra performance liquid chromatography [SE-UPLC]), such that native means non-aggregated and non-degraded. 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 defined temperature. The defined amount of time after which stability is measured can be at least 14 days, 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, or more. The defined 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. For example, a pharmaceutical formulation may be deemed stable if after 6 months of storage at 5ºC, greater than about 95%, 96%, 97% or 98% of native antibody is detected by SE-UPLC. A pharmaceutical formulation may also

be deemed stable if after 6 months of storage at 25ºC, greater than about 95%, 96%, 97% or 98% of native antibody is detected by SE-UPLC. A pharmaceutical formulation may also be deemed stable if after 28 days of storage at 40ºC, greater than about 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, or 98% of native antibody is detected by SE-UPLC. A pharmaceutical formulation may also be deemed stable if after 12 months of storage at -20ºC, greater than about 96%, 97%, or 98% of native antibody is detected by SE-UPLC. A pharmaceutical formulation may also be deemed stable if after 12 months of storage at -30ºC, greater than about 96%, 97% or 98% of native antibody is detected by SE-UPLC. A pharmaceutical formulation may also be deemed stable if after 12 months of storage at -80ºC, greater than about 96%, 97% or 98% of native antibody is detected by SE-UPLC.

[0109] Stability can be measured, *inter alia*, by determining the percentage of antibody that forms in an aggregate within the formulation after storage for a defined amount of time at a defined temperature, 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 ultra performance liquid chromatography [SE-UPLC]). An "acceptable degree of stability", as that phrase is used herein, means that at most 5% of the antibody is in an aggregated form (also denoted as the high molecular weight – HMW – form) detected in the formulation after storage for a defined amount of time at a given temperature. In certain embodiments an acceptable degree of stability means that at most about 5%, 4%, 3%, 2%, 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. 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, 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. For example, a pharmaceutical formulation may be deemed stable if after 12 months of storage at 5ºC, less than about 2%, 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 three months of storage at 25ºC, less than about 4%, 3%, 2%, 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 28 days of storage at 45ºC, less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or 0.5%, 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 3%, 2%, 1%, 0.5%, or 0.1% of the antibody is detected in an aggregated form.

[0110] Stability can 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, *inter alia*, ion exchange chromatography (*e.g.*, cation exchange ultra performance liquid chromatography [CEX-UPLC]). An "acceptable degree of stability", as that phrase is used herein, means that at most 45% of the antibody is in a more acidic form detected in the formulation after storage for a defined amount of time at a defined temperature. In certain embodiments an acceptable degree of stability means that at most about 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. In one embodiment, an acceptable degree of stability means that less than 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, 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, or about 45ºC. For example, a pharmaceutical formulation may be deemed stable if after three months of storage at -80ºC, -30ºC, or -20ºC less than about 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or 0.1% of the antibody is in a more acidic form. A pharmaceutical formulation may also be deemed stable if after six months of storage at 5ºC, less than about 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or 0.1% of the antibody is in a more acidic form. A pharmaceutical formulation may also be deemed stable if after six months of storage at 25ºC, less than about 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or 0.1% of the antibody is in a more acidic form. A pharmaceutical formulation may also be deemed stable if after 28 days of storage at 45ºC, less than about 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or 0.1% of the antibody can be detected in a more acidic form.

[0111] Other methods may be used to assess the stability of the formulations of the present disclosure such as, *e.g.*, differential scanning calorimetry (DSC) to determine thermal stability, controlled agitation to determine mechanical stability, and absorbance at about 350 nm or about 405 nm to determine solution turbidities. For example, a formulation of the present disclosure may be considered stable if, after 6 or more months of storage at about 5ºC to about 25ºC, the change in OD_{405} of the formulation is less than about 0.05 (*e.g.*, 0.04, 0.03, 0.02, 0.01, or less) from the OD_{405} of the formulation at time zero.

[0112] Measuring the biological activity or 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.*, 5ºC, 25ºC, 45ºC, etc. for a defined amount of time (*e.g.*, 1 to 12 months), the antibody contained within the formulation binds

to its antigen with an affinity that is at least 90%, 95%, or more of the binding affinity of the antibody prior to said storage. Binding affinity may be determined by *e.g.,* ELISA or surface plasmon resonance. Biological activity may be determined by an antibody activity assay, such as *e.g.,* contacting a cell that expresses LAG-3 or PD-1 with the formulation comprising the anti-LAG-3 antibody or anti-PD-1 antibody, respectively. The binding of the antibody to such a cell may be measured directly, such as *e.g.,* via FACS analysis. Alternatively, the downstream activity of a given ligand/receptor system may be measured in the presence of the antibody, and compared to the activity of the system in the absence of antibody. In some embodiments, the antigen to which the antibody binds may be endogenous to the cell. In other embodiments, the antigen may be ectopically expressed in the cell.

[0113] Additional methods for assessing the stability of an antibody in formulation are demonstrated in the Examples presented below.

[0114] The liquid pharmaceutical formulations of the present disclosure may, in certain embodiments, exhibit low to moderate levels of viscosity. "Viscosity" as used herein may be "kinematic viscosity" or "absolute viscosity". "Kinematic viscosity" is a measure of the resistive flow of a fluid under the influence of gravity. When two fluids of equal volume are placed in identical capillary viscometers and allowed to flow by gravity, a viscous fluid takes longer than a less viscous fluid to flow through the capillary. For example, if one fluid takes 200 seconds to complete its flow and another fluid takes 400 seconds, the second fluid is twice as viscous as the first on a kinematic viscosity scale. "Absolute viscosity", sometimes called dynamic or simple viscosity, is the product of kinematic viscosity and fluid density (Absolute Viscosity = Kinematic Viscosity x Density). The dimension of kinematic viscosity is L^2/T where L is a length and T is a time. Commonly, kinematic viscosity is expressed in centistokes (cSt). The SI unit of kinematic viscosity is mm^2/s, which is 1 cSt. Absolute viscosity is expressed in units of centipoise (cP). The SI unit of absolute viscosity is the milliPascal-second (mPa-s), where 1 cP = 1 mPa-s.

[0115] As used herein, a low level of viscosity, in reference to a fluid formulation of the present disclosure, will exhibit an absolute viscosity of less than about 20 cPoise (cP). For example, a fluid formulation of the invention will be deemed to have "low viscosity", if, when measured using standard viscosity measurement techniques, the formulation exhibits an absolute viscosity of about 20 cP, about 19 cP, about 18 cP, about 15 cP,

about 12 cP, about 10 cP, about 9 cP, about 8 cP, or less. As used herein, a moderate level of viscosity, in reference to a fluid formulation of the present disclosure, will exhibit an absolute viscosity of between about 35 cP and about 20 cP. For example, a fluid formulation of the invention will be deemed to have "moderate viscosity", if when measured using standard viscosity measurement techniques, the formulation exhibits an absolute viscosity of about 34 cP, about 33 cP, about 32 cP, about 31 cP, about 30 cP, about 29 cP, about 28 cP, about 27 cP, about 26 cP, about 25 cP, about 24 cP, about 23 cP, about 22 cP, about 21 cP, about 20 cP, about 19 cP, 18 cP, about 17 cP, about 16 cP, or about 15 cP.

[0116] In some aspects, as illustrated in the examples below, the present inventors have made the surprising discovery that stable formulations comprising high concentrations of an anti-human LAG-3 antibody in combination with an anti-PD-1 antibody (*e.g.*, 57.4 mg/ml and 75 mg/ml total antibody) can be obtained by formulating the antibodies with arginine hydrochloride from about 15 mM to about 20 mM and sucrose at about 9% or about 9.7%. Such formulations are stable to stress during handling and to storage at temperatures ranging from 5°C to 45°C (shown herein).

EXEMPLARY FORMULATIONS

[0117] According to one aspect of the present disclosure, the pharmaceutical formulation is a stable, generally physiologically isotonic liquid formulation, which comprises an anti-LAG3 antibody (mAb1) and an anti-PD-1 antibody (mAb2), a histidine buffer system that provides sufficient buffering at about pH 6.0 ± 0.3; an organic cosolvent, which protects the structural integrity of the antibody; a thermal stabilizer that is a sugar; and one or more amino acids, which serve to retain stability, and maintain tonicity of the formulation for injection in a convenient volume, e.g., formulation suitable for intravenous administration.

[0118] According to one aspect of the present disclosure, the stable pharmaceutical formulation comprises: (a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody; mAb1) or antigen-binding fragment thereof, (b) anti-human programmed death 1 antibody (anti-PD-1 antibody; mAb2) or antigen-binding fragment thereof, (c) a buffer, (d) a sugar, (e) a non-ionic surfactant, and (f) an amino acid, at pH 6.0 ± 0.3, wherein: the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain

complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 1 and LCVR that comprises the amino acid sequence of SEQ ID NO: 2. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody HCVR that comprises the amino acid sequence of SEQ ID NO: 11 and LCVR that comprises the amino acid sequence of SEQ ID NO: 12. In some aspects, the stable pharmaceutical formulation as described herein comprises an anti-LAG3 antibody that 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 aspects, the stable pharmaceutical formulation as described herein comprises an anti-PD-1 antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0119] In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from 20 mg/ml to 60 mg/ml, or from 35 mg/ml to 52 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 40 mg/ml ± 10 mg/ml. In some aspects, the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 47.1 mg/ml ± 10 mg/ml.

[0120] In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from 5 mg/ml to 50 mg/ml, or from 9 mg/ml to 40 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 10.3 mg/ml ± 2 mg/ml. In some aspects, the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 35 mg/ml ± 4 mg/ml.

[0121] The buffer can be phosphate buffer, acetate buffer, or histidine buffer. In some aspects, the buffer is phosphate buffer. In some aspects, the buffer is acetate buffer. In some aspects, the buffer is histidine buffer. The buffer concentration can range from about 5 mM to about 20 mM. In some aspects, the buffer concentration is 10 mM ± 2 mM.

[0122] Sugar is present in the pharmaceutical formulation at a concentration of from about 5% to about 12% w/v, or at a concentration of about 9% ± 2% w/v or about 9.7% ± 2% w/v. In some aspects, the sugar is sucrose.

[0123] The stable pharmaceutical formulation comprises a non-ionic surfactant, for example, polysorbate. In some aspects, the non-ionic surfactant is present at a concentration of from 0.08% to 0.22% w/v. In some aspects, the non-ionic surfactant is present at a concentration of 0.1% ± 0.025% w/v. In some aspects, the non-ionic surfactant is polysorbate 80 and is present at a concentration of 0.1% ± 0.025% w/v.

[0124] The stable pharmaceutical formulation comprises an amino acid, for example, arginine or/or proline. In some aspects, the amino acid is arginine. In some aspects, the amino acid is proline. In some aspects, the amino acid is arginine and proline. In some aspects, the arginine is present at a concentration of from 12mM to 23mM. In some aspects, the arginine is present at a concentration of 16mM ± 4mM. In some aspects, the arginine is present at a concentration of 18.8mM ± 4mM. In some aspects, the proline is present at a concentration of from 0.07mM to 0.36mM. In some aspects, the proline is present at a concentration of 0.09mM ± 0.02mM. In some aspects, the proline is present at a concentration of 0.3mM ± 0.06mM.

[0125] Provided herein are stable pharmaceutical formulations comprising: (a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof, (b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof, (c) 10mM ± 2mM histidine, (d) 9.7% ± 2% w/v sucrose, (e) 0.11% ± 0.03% w/v polysorbate 80, (f) 18.8mM ± 4mM arginine, and (g) 0.09% ± 0.02% w/v

proline, at pH 6.0 ± 0.3; wherein: the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18. The anti-LAG3 antibody or antigen-binding fragment thereof is present in the formulation at a concentration of about 47.1 mg/mL ± 10 mg/ml and the anti-PD-1 antibody or antigen-binding fragment thereof is present in the formulation at a concentration of about 10.3 mg/mL ± 1.0 mg/ml.

[0126] Also provided herein are stable pharmaceutical formulations comprising: (a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof, (b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof, (c) 10mM ± 2mM histidine, (d) 9.0% ± 2% w/v sucrose, (e) 0.12% ± 0.03% w/v polysorbate 80, (f) 16mM ± 4mM arginine, and (g) 0.3% ± 0.06% w/v proline, at pH 6.0 ± 0.3; wherein: the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3

comprises the amino acid sequence of SEQ ID NO: 8, and the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18. The anti-LAG3 antibody or antigen-binding fragment thereof is present in the formulation at a concentration of about 40.0 mg/mL ± 10 mg/ml and the anti-PD-1 antibody or antigen-binding fragment thereof is present in the formulation at a concentration of about 35.0 mg/mL ± 4.0 mg/ml.

[0127] According to one embodiment, the stable pharmaceutical formulation comprises: (i) a human IgG4 antibody that specifically binds to human LAG-3 (mAb1), and which comprises an HCDR1 of SEQ ID NO: 3, an HCDR2 of SEQ ID NO: 4, an HCDR3 of SEQ ID NO: 5, an LCDR1 of SEQ ID NO: 6, an LCDR2 of SEQ ID NO: 7, and an LCDR3 of SEQ ID NO: 8, in an amount of 1600 mg or 400 mg, a human IgG4 antibody that specifically binds to PD-1 (mAb2), and which comprises an HCDR1 of SEQ ID NO: 13, an HCDR2 of SEQ ID NO: 14, an HCDR3 of SEQ ID NO: 15, an LCDR1 of SEQ ID NO: 16, an LCDR2 of SEQ ID NO: 17, and an LCDR3 of SEQ ID NO: 18, in an amount of 350 mg. In some embodiments, the total concentration of mAb1 and mAb2 in the co-formulation is 57.4 mg/ml ± 10 mg/ml. In some embodiments, the total concentration of mAb1 and mAb2 in the co-formulation is 75 mg/ml ± 10 mg/ml.

[0128] Additional non-limiting examples of pharmaceutical formulations encompassed by the present invention are set forth elsewhere herein, including the working Examples presented below.

CONTAINERS AND METHODS OF ADMINISTRATION

[0129] 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, or bottle. 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 or administer the pharmaceutical formulations of the present disclosure.

[0130] 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 or equal to 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.

[0131] 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, 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 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). FluroTec® is an example of a fluorocarbon coating used to minimize or prevent drug product from adhering to the rubber surfaces.

[0132] 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.

[0133] 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 or oral administration. Numerous reusable pen 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). Examples of disposable pen or autoinjector delivery devices having applications in subcutaneous delivery of a pharmaceutical formulation 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).

[0134] The use of a microinfusor to deliver the pharmaceutical formulations of the present disclosure is also contemplated herein. As used herein, the term "microinfusor" means a subcutaneous delivery device designed to slowly administer large volumes (*e.g.*, up to about 2.5 mL or more) of a therapeutic formulation over a prolonged period of time (*e.g.*, about 10, 15, 20, 25, 30 or more minutes). *See, e.g.*, U.S. 6,629,949; US 6,659,982; and Meehan *et al.*, *J. Controlled Release 46*:107-116 (1996). Microinfusors are particularly useful for the delivery of large doses of therapeutic proteins contained within high concentration (*e.g.*, about 100, 125, 150, 175, 200 or more mg/mL) or viscous solutions.

[0135] In certain embodiments, the stable pharmaceutical formulation of any of the preceding aspects is contained in a sterile glass vial and is administered as an IV infusion.

[0136] In one embodiment, the container is a 20 mL type 1 clear borosilicate glass vial. In certain embodiments, the container is a 2 mL, 5mL, 10 mL, or 20 mL type 1 borosilicate glass vial with a chlorobutyl stopper, with a FluroTec® coating.

[0137] In one embodiment, the liquid pharmaceutical formulation of the present disclosure comprising about 57.4 mg/mL total antibody is administered intravenously and may be contained in a glass vial.

[0138] In one embodiment, the liquid pharmaceutical formulation of the present disclosure comprising about 75 mg/mL of total antibody is administered intravenously and may be contained in a glass vial.

[0139] In certain embodiments, the present disclosure provides an autoinjector comprising any of the stable formulations described herein. In some embodiments, the present disclosure provides an autoinjector comprising a stable formulation comprising about 57.4 mg/mL, about 75 mg/mL, about 100 mg/mL, about 150 mg/mL, or about 175 mg/mL of total antibody, about 10mM of histidine, at pH of about 6.0, about 9% sucrose or about 9.7% sucrose, about 16 mM or about 18.8 mM arginine hydrochloride, about 0.09% w/v or about 0.3% w/v proline, and about 0.11% polysorbate 80 or about 0.12% polysorbate 80.

[0140] In certain embodiments, the present disclosure provides a prefilled syringe comprising any of the stable formulations described herein. In some embodiments, the present disclosure provides a prefilled syringe comprising a stable formulation comprising about 57.4 mg/mL, about 75 mg/mL, about 100 mg/mL, about 150 mg/mL or about 175 mg/mL of total antibody, about 10mM of histidine, at pH of about 6.0 ± 0.3, 9% sucrose or about 9.7% sucrose, about 16 mM or about 18.8 mM arginine hydrochloride, about 0.09% w/v or about 0.3% w/v proline, and about 0.11% polysorbate 80 or about 0.12% polysorbate 80. In certain embodiments, the syringe is a 1 mL or 2.25 mL long glass syringe filled with a 27-gauge thin wall needle, a fluorocarbon coated rubber plunger and a rubber needle shield.

[0141] In one embodiment, the stable pharmaceutical formulation containing about 57.4 mg/mL ± 10 mg/mL total antibody is administered in a volume of approximately up to 2

mL in a prefilled syringe. In one embodiment, the stable pharmaceutical formulation containing about 75 mg/mL ± 10 mg/mL total antibody is administered in a volume of approximately up to 2 mL in a prefilled syringe. In certain embodiments, the syringe is a 1 mL or 2.25 mL long glass syringe filled with a 27-gauge thin wall needle, a fluorocarbon coated rubber plunger and a rubber needle shield. In one embodiment, the syringe is an OMPI 1 mL long glass syringe fitted with a 27-gauge needle, a FM27 rubber needle shield, and a FLUROTEC® coated 4023/50 rubber plunger.

THERAPEUTIC USES OF THE PHARMACEUTICAL FORMULATIONS

[0142] The pharmaceutical formulations of the present disclosure are useful, *inter alia*, for the treatment, prevention or amelioration of any disease or disorder associated with PD-1 and LAG-3 activity, including diseases or disorders mediated by PD-1 and LAG-3. Exemplary, non-limiting diseases and disorders that can be treated or prevented by the administration of the pharmaceutical formulations of the present disclosure include viral infections, autoimmune diseases and various cancers such as, *e.g.*, brain cancer, lung cancer, prostate cancer, colorectal cancer, head and neck cancer, skin cancer, various blood cancers, and endometrial cancers.

EXAMPLES

[0143] The following examples are presented 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 formulations 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 mole, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric pressure.

Example 1: Development of an anti-LAG-3/anti-PD-1 antibody coformulation

[0144] The goals of the formulation activities were to develop a coformulation with the following attributes:

- A stable formulation with a concentration of the anti-LAG-3 antibody (mAb1) sufficient to deliver a dose of 400 mg or 1600 mg and a concentration of the anti-PD-1 antibody (mAb2) sufficient to deliver a dose of 350 mg;
- A near iso-osmolar formulation that is stable upon dilution with commonly used diluents, *e.g.*, 0.9% sodium chloride injection or 5% dextrose injection, for intravenous infusion;
- A formulation that is compatible with and stable in Type 1 clear glass vial and standard serum stopper as packaging; and
- A sterile drug product (DP) solution that supports long-term stability;
    - A formulation that minimizes antibody high molecular weight (HMW) species when subjected to handling and thermal stresses;
    - A formulation that minimizes new impurities when antibodies are combined, e.g., heterodimer formation;
    - A formulation that minimizes changes in the relative distribution of antibody charged species when subjected to thermal stress; and
    - A formulation that maintains biological activity when subjected to handling and thermal stress.

[0145] Throughout formulation development, three primary protein stress conditions (representing extreme handling conditions beyond which the antibody drug product would not be subjected during handling, manufacturing, shipping, storing, and labeling) were employed to develop and optimize the antibody formulations and to evaluate the effects of potential real-world stresses on the stability of the drug product. These stress conditions included:

- Agitation (vortexing) of the protein solution at room temperature. Vortexing in glass vials exceeds the agitation that occurs during the handling and manufacturing of the protein.
- Incubating the protein solution at elevated temperature (37°C, 40°C or 45°C) relative to the proposed DP storage condition (2°C-8°C).
- Subjecting the protein to multiple freeze thaw cycles. Since the protein will undergo at least one freeze thaw cycle during the manufacture of DP, multiple freeze thaw cycles simulate and exceed the actual stress the protein is expected to experience.

[0146] Other attributes of the formulations will be apparent from the description herein.

Anti-LAG-3 Antibodies:

[0147] Anti-LAG-3 antibodies are described in U.S. 10,358,495, incorporated herein in its entirety. The exemplary antibody used in the Examples below is a fully human anti-LAG-3 antibody known as "REGN3767" or "Fianlimab" (referred to herein as mAb1) comprising three heavy chain complementarity determining regions (HCDRs) within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 1 and three light chain complementarity determining regions (LCDRs) within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 2; or an HCVR/LCVR amino acid sequence pair comprising SEQ ID NOs: 1/2; or heavy and light chain CDR sequences comprising SEQ ID NOs: 3 – 8; or three heavy chain CDRs within a heavy chain amino acid sequence of SEQ ID NO: 9 and three light chain CDRs within a light chain amino acid sequence of SEQ ID NO: 10; or a heavy chain amino acid sequence of SEQ ID NO: 9 and a light chain amino acid sequence of SEQ ID NO: 10. The antibody possesses an approximate molecular weight of about 145 kDa and the heavy chain possesses an IgG4 isotype constant region.

Anti-PD-1 Antibodies:

[0148] Anti-PD-1 antibodies are described in U.S. 9,987,500, incorporated herein in its entirety. The exemplary antibody used in the Examples below is a fully human anti-PD-1 antibody known as "REGN2810" or "Cemiplimab" (referred to herein as mAb2) comprising three heavy chain complementarity determining regions (HCDRs) within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 11 and three light chain complementarity determining regions (LCDRs) within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 12; or an HCVR/LCVR amino acid sequence pair comprising SEQ ID NOs: 11/12; or heavy and light chain CDR sequences comprising SEQ ID NOs: 13 – 18; or three heavy chain CDRs within a heavy chain amino acid sequence of SEQ ID NO: 19 and three light chain CDRs within a light chain amino acid sequence of SEQ ID NO: 20; or a heavy chain amino acid sequence of SEQ ID NO: 19 and a light chain amino acid sequence of SEQ ID NO: 20. The antibody possesses an approximate molecular weight of about 146 kDa and the heavy chain possesses an IgG4 isotype constant region.

[0149] Co-formulated mAb1 and mAb2 were evaluated for intravenous (IV) administration in clinical studies.

Example 2: Exemplary Formulations

[0150] In certain embodiments, mAb1 and mAb2 are co-formulated as an aqueous buffered formulation containing a buffer, a sugar, a non-ionic surfactant, and an amino acid, at pH 6.0 ± 0.3. Exemplary formulations include (1) 10 mM ± 2 mM histidine buffer, 9.7% w/v ± 2% w/v sucrose, 0.11% w/v ± 0.03% w/v polysorbate 80, 18.8 mM ± 4 mM arginine hydrochloride, and 0.09% w/v ± 0.02% w/v proline, at pH 6.0 ± 0.3; and (2) 10 mM ± 2 mM histidine buffer, 9% w/v ± 2% w/v sucrose, 0.12% w/v ± 0.03% w/v polysorbate 80, 16 mM ± 4 mM arginine hydrochloride, and 0.3% w/v ± 0.06% w/v proline, at pH 6.0 ± 0.3. Surprisingly, coformulations comprising both mAb1 and mAb2, previously formulated separately with different excipient and excipient concentrations, are stable and exhibit low heterodimer formation under stress over time. And, unexpectedly, proline and arginine were found to be compatible in the stable formulations as disclosed herein.

[0151] In some embodiments, the coformulation comprises:

(a) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(c) sucrose at a concentration of no more than about 250 mg/ml,

(d) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(e) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(f) proline at a concentration of no more than about 2 mg/ml, and

(i) water for Injection, USP, at pH 6.0 ± 0.3.

[0152] In some embodiments, the coformulation comprises:

(a) a buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.5 mg/ml,

(c) sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml,

(d) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(e) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1.0 mg/ml, and

(f) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.20 mg/ml.

[0153] In some embodiments, the coformulation comprises:

(a) a buffer comprising histidine at a concentration of about 0.74 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(c) sucrose at a concentration of about 97 mg/ml,

(d) polysorbate 80 at a concentration of about 1.1 mg/ml,

(e) arginine hydrochloride at a concentration of about 4 mg/ml, and

(f) proline at a concentration of about 0.9 mg/ml.

[0154] In some embodiments, the concentration of mAb1 in the coformulation is 47.1 mg/ml ± 5 mg/ml. In some embodiments, the concentration of mAb2 in the coformulation is 10.3 mg/ml ± 1 mg/ml. In some embodiments, the total concentration of mAb1 and mAb2 in the co-formulation is 57.4 mg/ml ± 10 mg/ml.

[0155] In some embodiments, the concentration of mAb1 in the coformulation is 40 mg/ml ± 10 mg/ml. In some embodiments, the concentration of mAb2 in the coformulation is 35 mg/ml ± 4 mg/ml. In some embodiments, the total concentration of mAb1 and mAb2 in the co-formulation is 75 mg/ml ± 10 mg/ml.

[0156] In some embodiments, mAb1 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In some embodiments, the stable pharmaceutical formulation as described herein comprises an mAb1 HCVR that comprises the amino acid sequence of SEQ ID NO: 1 and LCVR that comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the stable

pharmaceutical formulation as described herein includes mAb1 comprising 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.

[0157] In some embodiments, mAb2 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18. In some embodiments, the stable pharmaceutical formulation as described herein comprises an mAb2 HCVR that comprises the amino acid sequence of SEQ ID NO: 11 and LCVR that comprises the amino acid sequence of SEQ ID NO: 12. In some embodiments, the stable pharmaceutical formulation as described herein includes mAb2 comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

Example 3: Methods Used to Assess Formulation Stability

[0158] The following assays were applied to assess formulation stability:

- Color and appearance by visual inspection
- pH using pH meter
- Turbidity measured by increase in optical density at 405nm or nephelometry
- Protein concentration by reversed-phase ultra performance liquid chromatography (RP-UPLC)
- Purity of DP was assessed using the following assays:
    - Size-exclusion ultra performance liquid chromatography (SE-UPLC)
    - Reduced and non-reduced microchip capillary electrophoresis (MCE)
- Charge variant analysis was determined using the following assays:
    - Cation exchange UPLC (CEX-UPLC)
    - Imaged capillary isoelectric focusing (iCIEF)

Charge variants are reported as percent Region 1, Region 2, Region 3, Region 4 and two Main Peaks. Region 1 corresponds to acidic species which elute before the REGN2810 main peak; Region 2 corresponds to the basic species which elute after the REGN2810 main peak; Region 3 corresponds to the acidic species which elute before the REGN3767 main peak; and Region 4 corresponds to basic species which elute after the REGN3767 main peak.

- Potency was assessed by bioassay: the relative potency of each sample was determined by bioassay and is defined as: (IC_{50} reference sample/IC_{50} sample) × 100%. The measured potency of storage stability samples must be within 50% – 150% of the measured potency of the reference standard.
- Subvisible particulates were measured by light obscuration (LO) and/or microflow-imaging (MFI).
- Polysorbate 80 content was measured by ultra-performance liquid chromatography (CAD-UPLC).
- Molecular ratio of mAb1/mAb2 was measured using hydrophobic interaction chromatography, reduced mobility capillary electrophoresis or mixed-mode size exclusion chromatography.
- The presence of heterodimers was assessed by SE-UPLC coupled with mass spectrometry.

[0159] The physical stability of a formulation refers to properties such as color, appearance, pH, turbidity, and protein concentration. The presence of visible particulates in solution can be detected by visual inspection. A solution passes visual inspection if it is clear to slightly opalescent, essentially free from visible particulates, and colorless to pale yellow. In addition, turbidity, measured by OD at 405 nm, can also be used to detect particulates in solution. An increase in OD at 405 nm may indicate the presence of particulates, an increase in opalescence, or color change of the test articles. MFI is used to measure subvisible particulates that are ≥ 2 µm in size. The protein concentration of mAb1/mAb2 is measured by a RP-UPLC assay and reported as percent protein recovery relative to the starting material. In the RP-UPLC assay, the antibody is eluted from the RP column as a single peak. The protein concentration is determined from the mAb1/mAb2 total peak area by comparing it with a calibration curve generated using

mAb1 standards. Percent of recovery is calculated based on the measured protein concentration relative to the starting protein concentration.

[0160] Chemical stability refers to the formation of covalently modified forms (e.g. covalent aggregates, cleavage products, or charge variant forms) and non-covalently modified forms (e.g. non-covalent aggregates) of protein. Higher and lower molecular weight degradation products can be separated from native mAb1/mAb2 by SE-UPLC and MCE-SDS methods. The percentage of degraded antibody in the SE-UPLC and MCE-SDS methods is calculated from the ratio of the area of all non-native peaks to the total area of all antibody peaks. Charge variant forms of mAb1/mAb2 are resolved using CEX-UPLC and iCIEF. In the CEX-UPLC method, peaks with retention times earlier than that of the main peak are labeled as "acidic" peaks; the peaks with retention times later than that of the main peak are labeled as "basic" peaks. In the iCIEF method, peaks that are focused to a pI lower than that of the main peak are labeled "acidic" peaks, whereas those focused to a pI higher than that of the main peak are labeled "basic" peaks.

Example 4: mAb1/mAb2 Co-formulated Drug Product (DP)

[0161] This Example refers to formulation development and related stability assessment for 400 mg:350 mg and 800 mg:175 mg REGN3767-2810 fixed dose combination (FDC) drug product (DP). The suitability of these formulations was confirmed by long-term stability studies. Due to the demonstrated stability and similarities in formulation composition (e.g. buffer, buffer concentration, pH, surfactant, and sucrose as stabilizer) of both 50 mg/mL REGN3767 (mAb1) and 175 mg/mL REGN2810 (mAb2) formulations, they were chosen as source material for manufacturing both FDC formulations. REGN3767 and REGN2810 FDS were combined at different volumetric ratios (4:1 and 16:1) to target clinical doses at or multiples of 800 mg REGN3767 + 175 mg REGN2810 or 400 mg REGN3767 + 350 mg REGN2810. mAb1 (REGN3767) and mAb2 (REGN2810) formulated drug substance (FDS) were combined at different volumetric ratios (4:1 and 16:1) to target clinical doses at or multiples of 800 mg mAb1 + 175 mg mAb2 (e.g., a total dose of 1600 mg mAb1 + 350 mg mAb2) or 400 mg mAb1 + 350 mg mAb2 (fixed dose combination drug product; FDC DP). Comparison of the fixed combination DPs in two versions are presented in Table 1. The final preparation of FDC

DP results in the same concentrations of mAb1 and mAb2 and near identical excipient concentrations compared with co-administered individual monoclonal antibodies (mAbs).

Table 1: mAb1/mAb2 Formulation Summary

Formulation Component	Fixed Combination Dose Drug Product	
	400 mg:350 mg mAb1:mAb2	800 mg:175 mg mAb1:mAb2
mAb1 concentration (mg/mL)	40.0	47.1
mAb2 concentration (mg/mL)	35.0	10.3
Total protein concentration (mg/mL)	75.0	57.4
L-histidine concentration (mM)	10.0	10.0
L-arginine hydrochloride (mM)	16.0	18.8
L-proline (%w/v)	0.30	0.09
Sucrose (%w/v)	9.0	9.7
Polysorbate 80 (%w/v)	0.12	0.11
pH	6.0	6.0

[0162] L-proline is a tonicifier. L-arginine hydrochloride is a tonicifier in both FDC formulations. Compatibility of L-arginine hydrochloride and L-proline in the FDC was assessed by accelerated and long-term stability studies (see Example 6 herein).

[0163] The suitability of these FDC formulations was assessed by long term stability studies and are provided in Example 6 herein. Main degradation pathways for mAb1 and mAb2 in both FDC DPs are the same as mono DP under thermal stress at 40 °C/75% RH. Risk of interactions between REGN3767 and REGN2810 to form new impurity such as heterodimer was assessed and characterized by size-exclusion ultra-performance liquid chromatography mass spectrometry (SE-UPLC-MS). Total heterodimer was quantified and found to be <0.15% after 12 months at 5 °C for both 400 mg:350 mg and 800 mg:175 mg mAb1/mAb2 DP.

Conclusions

[0164] The 800mg:175mg REGN3767-2810 FDC DP contains 57.4 mg/mL combined protein; 47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM histidine, 9.7% w/v sucrose, 18.8 mM arginine hydrochloride, 0.09% w/v L-proline, and 0.11% w/v

polysorbate 80, at pH 6.0; the 400mg:350mg REGN3767-2810 FDC DP contains 75.0 mg/mL combined protein; 40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0 % w/v sucrose, 16.0 mM L-arginine HCl, 0.30% w/v L-proline, 0.12% w/v polysorbate 80, pH 6.0, 10 mM histidine, 9% w/v sucrose, 16 mM arginine hydrochloride, 0.03% w/v L-proline, and 0.12% w/v polysorbate 80, at pH 6.0. Coformulated DP demonstrated no significant hetero-interactions between mAb1 and mAb2, with minimal heterodimer formation.

[0165] Both the FDCs were compared with the R3767 and R2810 formulations. Based on the current assessment of protein quality attributes and stability trends, the 800 mg:175 mg and 400 mg:350 mg REGN3767-2810 FDC DPs are comparable with equivalent characteristics of individual REGN3767 and REGN2810 DP and there is no anticipated impact to product quality or stability by the addition of the coformulation manufacturing step. Surprisingly, both molecules were comparably stable despite having very different compositions as individual DPs. Further, the heterodimer was unexpectedly very low in both FDC formulations.

Overages

[0166] There are no overages included in the formula.

[0167] A slight overfill is included to compensate for the normal variations in fill volume encountered during an automated fill finish process and to ensure that the correct volume can be withdrawn from the vials.

Example 5: A Phase 3 trial of fixed dose combinations of fianlimab (anti-LAG-3) + cemiplimab (anti-PD-1) versus relatlimab + nivolumab in patients with unresectable or metastatic melanoma

[0168] Background: Fianlimab (anti-lymphocyte activation gene 3 [LAG-3]) and cemiplimab (anti–programmed cell death-1 [PD-1]) are high-affinity, fully human, immunoglobulin G4 monoclonal antibodies. In a multicohort phase 1 study (NCT03005782), fianlimab + cemiplimab demonstrated reproducibly high clinical activity (objective response rate [ORR]: 61%, N=98) in three independent cohorts of advanced PD-(ligand)1-naïve metastatic Mel patients with an acceptable safety profile.

[0169] Methods: This is a randomized, open-label, multicenter phase 3 study comparing the fixed dose combination (FDC) of fianlimab + cemiplimab to the FDC of relatlimab + nivolumab in patients with unresectable or metastatic melanoma. The

primary objective is to demonstrate superiority of fianlimab + cemiplimab compared with relatlimab + nivolumab as measured by ORR assessed by blinded independent central review (BICR).

[0170] Key inclusion criteria are: (1) aged ≥18 years; (2) histologically confirmed unresectable stage III or IV (metastatic) melanoma; (3) no prior systemic therapy for unresectable or metastatic Mel; (4) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (5) Eastern Cooperative Oncology Group (ECOG) performance status of ≤1; (6) adequate bone marrow, hepatic, and kidney function.

[0171] Approximately 560 patients are randomized in a 1:1 ratio to two treatment arms:

- Arm A: FDC of fianlimab 1600 mg + cemiplimab 350 mg every 3 weeks intravenously (IV);
- Arm B: FDC of relatlimab 160 mg + nivolumab 480 mg every 4 weeks IV.

[0172] Patients are stratified based on metastatic stage (stage III vs M1a–b vs M1c–d), baseline lactate dehydrogenase level (≤ vs > upper limit of normal), and prior adjuvant and/or neoadjuvant systemic therapy. Patients receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, a study withdrawal criterion is met, or the sponsor terminates the study.

[0173] The primary endpoint is ORR assessed by BICR. Key secondary endpoints are PFS assessed by BICR and overall survival. Additional secondary endpoints are duration of response, disease control rate, investigator-assessed ORR and PFS, safety, pharmacokinetics, and immunogenicity.

Example 6: Research Stability of the fixed dose formulations

[0174] This Example summarizes the research stability study for REGN3767-2810 Fixed Dose Combination (FDC) liquid Drug Products (DPs). There are two presentations of the REGN3767-2810 FDC DP (800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810).

[0175] The 800mg:175mg REGN3767-2810 FDC DP contains 57.4 mg/mL combined protein; 47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7 % w/v sucrose, 18.8 mM L-arginine HCl, 0.09% w/v L-proline, 0.11% w/v polysorbate 80, pH 6.0. The 400mg:350mg REGN3767-2810 FDC DP contains 75.0 mg/mL combined protein; 40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0 % w/v

sucrose, 16.0 mM L-arginine HCl, 0.30% w/v L-proline, 0.12% w/v polysorbate 80, pH 6.0. Both DPs are stored in 20R Schott Type 1 borosilicate glass vials. These DPs support the requirements for late-stage clinical development.

[0176] This stability study evaluates the stability of the REGN3767-2810 FDC DPs under long-term, accelerated, and stress conditions. For 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 FDC DPs, no appreciable changes in stability are detected during long-term storage at 2-8°C for up to 24 months in any of the monitored attributes. Results from this study support the recommended long-term storage condition of 2-8°C for both REGN3767-2810 FDC DPs.

[0177] The REGN3767 and REGN2810 FDS lots used to manufacture co-FDS development lots for this study are representative of the FDS manufactured for clinical use but were produced at a smaller scale. The fill volumes and container/closure size and type tested are identical to the fill volumes and container/closure size and type that were used to manufacture the clinical DPs. The DPs were incubated under long-term storage, accelerated, and stress conditions. The accelerated and stress conditions were selected to simulate the conditions beyond which the DPs will not be subjected during manufacturing and handling, and to elucidate the degradation pathways for REGN3767-2810 FDC DPs.

[0178] The study was staged under the conditions described above: Long term storage condition: 2-8°C, up to 60 months; Accelerated condition: 25°C/60%RH, up to 6 months; Stressed condition: 40°C/75% RH, up to 3 months; Stressed condition: agitation by vortexing at 1000 RPM for up to 120 minutes; Stressed condition: freezing (-30°C) and thawing (room temperature) up to 4X cycles

[0179] In summary, the 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 FDC DPs were physically and chemically stable when stored at storage condition (2-8°C) for at least 24 months. No appreciable changes in any of the monitored attributes were detected at the storage condition of 2-8°C. All attributes examined meet FDG quality target under storage condition.

[0180] In this research stability study, the 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 FDC DPs were produced in 20R Type 1 borosilicate glass vials. The study design in Table 2 describes the various long-term storage,

accelerated, and stress conditions and the duration of time points being examined in the study.

Table 2: Research Stability Study Design and Conditions

Conditions	Storage Temperature	Length of Storage	
Storage	5°C	0, 1, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months	Container Closure: 20R Schott Type 1 Borosilicate Glass Vial with 20 mm Liquid Stopper
Accelerated	25°C/60% RH	0, 0.5, 1, 3 and 6 months	
Thermal Stress	40°C/75% RH	0, 0.25, 0.5, 1, and 3 months	
Stress	Agitation	0, 60, and 120 minutes	
	Freezing and Thawing	0, 2, and 4 cycles	

[0181] Table 3 summarizes the materials used in the study.

Table 3

Material	Description
FDC for 800mg:175mg REGN3767-2810	47.06 mg/mL REGN3767, 10.29 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) Sucrose, 18.8 mM l-arginine HCl, 0.088% (w/v) L-proline, 0.11% (w/v) polysorbate 80 (SR), pH 6.0
FDC for 400mg:350mg REGN3767-2810	40 mg/mL REGN3767, 35 mg/mL REGN2810, 10 mM L-histidine, 9% (w/v) Sucrose, 16 mM L-arginine HCl, 0.3% (w/v) L-proline, 0.12% (w/v) polysorbate (SR), pH 6.0
Glass Vial	Schott 20R Type 1 Borosilicate Glass Vial
Liquid Stopper	20 mm West Liquid Stopper: S10-F4514432/50G B2-40
Filter	0.22 µm PVDF Stericup Filter

[0182] The methods used to analyze the stability study of REGN3767-2810 FDC DPs are listed in Table 4.

Table 4: Analytical testing plan

Quality Attributes/Assay	Testing Timepoints for stability studies
Appearance	All timepoints
pH	
Protein Conc. by SoloVPE®	
Purity by SE-UPLC	
Purity by MCE (Reducing and Non-Reducing)	

Charge Heterogeneity by iCIEF	
Potency by Bioassay	t=0 6, 12, 24, 36, 48, and 60 months for 5°C 6 months for 25°C/60%RH 3 months for 40ºC/75%RH 120 minutes vortex 4 cycles freeze / thaw
Particulate matter by MFI™	t=0 3, 6, 12, 24, 36, 48, and 60 months for 5°C 3, 6 months for 25°C/60%RH 3 months for 40ºC/75%RH 120 minutes vortex 4 cycles freeze / thaw
Particulate matter by LO	
Polysorbate content by CAD	t=0 6, 12, 24, 36, 48, and 60 months for 5°C 6 months for 25°C/60%RH 3 months for 40ºC/75%RH
Molecular Ratio by HIC	t=0 6, 12, 24, 36, 48, and 60 months for 5°C 6 months for 25°C/60%RH 3 months for 40ºC/75%RH 120 minutes vortex 4 cycles freeze / thaw
Aggregation by SE-MS	t=0 1 3, 6, 12, and 24 months for 5°C 1, 3, 6 months for 25°C/60%RH 1, 3, months for 40ºC/75%RH

[0183] Long-term storage stability: Both FDC DP were physically and chemically stable when stored at long-term storage condition (2-8°C) for at least 24 months (see Table 8 for the 800mg:175mg REGN3767-2810 FDC DP, Table 11 for the 400mg:350mg REGN3767-2810 FDC DP). No appreciable changes in stability were detected in any of the monitored attributes at 2-8°C in 20R vials. These results indicate that the 800mg:175mg REGN3767-2810 FDC DP and 400mg:350mg REGN3767-2810 FDC DP are stable for at least 24 months at storage conditions.

[0184] Thermal Accelerated and Stress Stability: Results from the analysis of the REGN3767-2810 FDC DPs after incubation under accelerated and stress thermal conditions are provided in Table 9 and Table 12.

[0185] No appreciable changes in the physical or chemical stability were detected after incubation at 25°C/60% RH for 1 month (Table 5), indicating both REGN3767-2810 FDC DPs can be exposed to room temperature for up to 1 month. After 6 months incubation at 25°C/60% RH, LMW species by MCE and formation of charge variants by iCIEF were detected as shown in Table 6. For details, refer to Table 9 and Table 12.

Table 5: Summary of Change in Stability of REGN3767-2810 FDC DP after Incubation at 25 °C/60%RH for 1 Month

FDC DP	Δ % HMW by SE-UPLC	Δ % LMW by Non-reduced MCE	Δ % Region 1C (REGN2810 Acidic Region) by iCIEF	Δ % Region 2C (REGN2810 Basic Region) by iCIEF	Δ % Region 3C (REGN3767 Acidic Region) by iCIEF	Δ % Region 4C (REGN3767 Basic Region) by iCIEF
800mg: 175mg	-0.2	0.3	-0.3	-0.1	0.6	2.4
400mg: 350mg	-0.1	0.1	2.6	0.2	2.6	1.9

Table 6: Summary of Change in Stability of REGN3767-2810 FDC DP after Incubation at 25 °C/60%RH for 6 Months

FDC DP	Δ % HMW by SE-UPLC	Δ % LMW by Non-reduced MCE	Δ % Region 1C (REGN2810 Acidic Region) by iCIEF	Δ % Region 2C (REGN2810 Basic Region) by iCIEF	Δ % Region 3C (REGN3767 Acidic Region) by iCIEF	Δ % Region 4C (REGN3767 Basic Region) by iCIEF
800mg: 175mg	0.0	1.1	1.2	0.6	9.0	5.2
400mg: 350mg	0.1	0.8	6.5	-1.2	3.9	5.1

Table 7: Summary of Change in Stability of REGN3767-2810 FDC DP after Incubation at 40 °C/75%RH for 3 Months

FDC DP	Δ % HMW by SE-UPLC	Δ % LMW by Non-reduced MCE	Δ % Region 1C (REGN2810 Acidic Region) by iCIEF	Δ % Region 2C (REGN2810 Basic Region) by iCIEF	Δ % Region 3C (REGN3767 Acidic Region) by iCIEF	Δ % Region 4C (REGN3767 Basic Region) by iCIEF
800mg: 175mg	2.2	2.2	6.3	-1.1	17.7	11.3
400mg: 350mg	3.0	2.8	17.5	-2.7	10.1	9.2

[0186] After incubation for 3 months at 40°C/75% RH, appreciable formation of HMW species by SE-UPLC, LMW species by MCE, and charge variants by iCIEF (illustrated in Table 7). For details, refer, see Table 9 and Table 12. The results from incubation under

accelerated and stress conditions demonstrated that an increase in HMW species, LMW species, and formation of charge variants were the main degradation pathways for REGN3767-2810 FDC DPs.

Table 8: Research Stability of 800mg:175mg REGN3767-2810 Fixed Dose Combination Drug Product Stored at 5°C

Formulation		**47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0**										
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**										
Fill Volume		**17.5 mL**										
Storage Condition		**5 °C**										
Assay		**Length of Storage (months)**										
		t=0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**	**60**
Physical form / Condition		LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP			
Clarity		Not > III	Not > III	Not > III	Not > III	Not > IV	Not > IV	Not > IV	Not > IV			
Color		Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6			
pH		6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0			
Total Protein (mg/mL)		58.4	57.8	57.0	57.3	58.8	59.3	58.3	59.8			
Potency (%)	REGN3767	94	NR	NR	134	NR	113	NR	90			
	REGN2810	100	NR	NR	73	NR	101	NR	86			
Reduced MCE (%)	Purity	95.1	95.4	95.1	94.9	94.9	95.1	95.6	96.0			
	NGHC	4.5	4.2	4.5	4.3	4.5	4.5	4.3	3.9			
	LMW	0.1	0.1	0.3	0.8	0.4	0.4	0.1	0.0			
Non-reduced MCE (%)	Purity	98.6	98.6	98.8	98.3	98.6	98.5	98.9	99.3			
	LMW	1.1	1.2	0.9	1.3	1.3	1.1	0.8	0.7			
SE-UPLC (%)	Purity	99.0	99.1	99.0	98.9	99.0	99.1	99.0	98.9			
	LMW	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0			
	HMW	1.0	0.9	1.0	1.1	1.0	0.8	1.0	1.1			
Heterodimer by SE-MS (%)		0.01	0.01	0.01	0.03	NR	0.08	0.05	0.08			
iCIEF (%)	Region 1C	5.5	5.0	5.1	5.5	4.8	5.1	4.7	4.9			
	REGN2810 Main Peak	10.4	10.8	10.3	11.3	10.7	11.0	10.5	10.6			
	Region 2C	2.2	2.0	1.8	2.0	1.8	2.0	1.9	1.7			
	Region 3C	21.3	21.3	21.2	19.6	20.4	18.9	22.1	22.5			
	REGN3767 Main Peak	52.9	53.6	52.5	53.4	54.3	54.1	51.4	51.4			
	Region 4C	7.8	7.4	8.4	8.2	8.2	8.9	9.5	8.8			
Particulate Analysis by LO (#/container)	≥ 10µm	143	NR	80	79	NR	68	NR	91			
	≥ 25µm	18	NR	0	0	NR	12	NR	12			
	2µm≤ x <10µm	233	NR	605	785	NR	611	NR	828			

Formulation		47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0										
Container Closure		20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal										
Fill Volume		17.5 mL										
Storage Condition		5 °C										
Assay		Length of Storage (months)										
		t=0	1	3	6	9	12	18	24	36	48	60
Particulate Analysis by MFI (#/mL)	≥ 10µm	2	NR	10	2	NR	30	NR	17			
	≥ 25µm	0	NR	0	2	NR	0	NR	2			
Polysorbate 80 (% w/v)		0.10	NR	NR	0.12	NR	0.12	NR	0.12			
REGN3767:REGN2810 Molecular Ratio by HIC		4.58	NR	NR	4.59	NR	4.56	NR	4.63			

Table 9: Research Stability of 800mg:175mg REGN3767-2810 Fixed Dose Combination Drug Product Stored at 25°C/60%RH or 40°C/75% RH

Formulation			47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0								
Container Closure			20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal								
Fill Volume			17.5 mL								
Assay			t=0	Storage at 25 °C/60% RH (months)				Storage at 40 °C/75% RH (months)			
				0.5	1	3	6	0.25	0.5	1	3
Physical form / Condition			LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP
Clarity			Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III
Color			Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6
pH			6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.1
Total Protein (mg/mL)			58.4	58.1	57.8	59.1	58.6	58.6	57.6	57.6	57.9
Potency (%)		REGN3767	94	NR	NR	NR	113	NR	NR	NR	98
		REGN2810	100	NR	NR	NR	98	NR	NR	NR	67
Reduced MCE (%)		Purity	95.1	95.5	95.3	94.4	94.0	94.9	94.8	93.8	91.0
		NGHC	4.5	4.1	4.2	5.1	5.4	4.5	4.6	5.4	7.0
		LMW	0.1	0.2	0.2	0.4	0.6	0.2	0.3	0.4	1.4
Non-reduced MCE (%)		Purity	98.6	98.5	98.3	98.7	97.5	98.4	98.2	97.4	96.0
		LMW	1.1	1.2	1.4	1.2	2.2	1.4	1.5	2.3	3.3
SE-UPLC (%)		Purity	99.0	99.2	99.2	99.1	99.0	99.0	99.0	98.6	96.7
		LMW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
		HMW	1.0	0.8	0.8	0.9	1.0	1.0	1.0	1.3	3.2
Heterodimer by SE-MS (%)			0.01	NR	0.02	0.04	0.06	NR	NR	0.09	0.25
iCIEF (%)	Region 1C		5.5	5.0	5.2	5.8	6.7	5.6	6.1	7.7	11.8
	REGN2810 Main Peak		10.4	10.5	10.2	9.6	8.8	10.4	9.7	8.2	4.0
	Region 2C		2.2	2.3	2.1	1.7	2.8	2.5	2.2	1.8	1.1

Formulation		**47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0**								
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**								
Fill Volume		**17.5 mL**								
Assay		**t=0**	**Storage at 25 °C/60% RH (months)**				**Storage at 40 °C/75% RH (months)**			
			0.5	**1**	**3**	**6**	**0.25**	**0.5**	**1**	**3**
	Region 3C	21.3	21.2	21.9	23.5	30.3	22.0	23.7	27.6	39.0
	REGN3767 Main Peak	52.9	52.0	50.3	47.1	38.3	48.8	45.2	38.1	25.0
	Region 4C	7.8	8.7	10.2	12.2	13.0	10.8	13.2	16.5	19.1
Particulate Analysis by LO (#/container)	≥ 10µm	143	NR	NR	33	62	NR	NR	NR	94
	≥ 25µm	18	NR	NR	0	0	NR	NR	NR	12
Particulate Analysis by MFI (#/mL)	2µm≤ x <10µm	233	NR	NR	189	574	NR	NR	NR	780
	≥ 10µm	2	NR	NR	5	15	NR	NR	NR	10
	≥ 25µm	0	NR	NR	0	2	NR	NR	NR	0
Polysorbate 80 (% w/v)		0.10	NR	NR	NR	0.12	NR	NR	NR	0.12
REGN3767:REGN2810 Molecular Ratio by HIC		4.58	NR	NR	NR	4.62	NR	NR	NR	4.92

Table 10: Research Stability of 800mg:175mg REGN3767-2810 Fixed Dose Combination Drug Product Effect of Agitation, and Freezing and Thawing

Formulation		**47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0**				
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**				
Fill Volume		**17.5 mL**				
Storage Condition		**Agitation: Vortex at 1000 rpm at room temperature** **Freezing/Thawing: Freeze at – 30 °C and thaw at room temperature**				
Assay		**t=0**	**Agitation (minutes)**		**Freezing/Thawing (cycles)**	
			60	**120**	**2**	**4**
Physical form / Condition		LEFVP	LEFVP	LEFVP	LEFVP	LEFVP
Clarity		Not > III	Not > III	Not > III	Not > III	Not > III
Color		Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6
pH		6.0	6.0	6.0	6.0	6.0
Total Protein (mg/mL)		58.4	57.8	57.6	58.4	57.5
Potency (%)	REGN3767	94	NR	75	97	NR
	REGN2810	100	NR	102	77	NR
Reduced MCE (%)	Purity	95.1	95.5	95.3	95.4	95.2
	NGHC	4.5	4.1	4.3	4.2	4.4
	LMW	0.1	0.1	0.1	0.1	0.1
Non-reduced MCE (%)	Purity	98.6	98.6	98.7	98.6	98.8

Formulation		**47.1 mg/mL REGN3767, 10.3 mg/mL REGN2810, 10 mM L-histidine, 9.7% (w/v) sucrose, 0.11% (w/v) polysorbate 80, 18.8 mM L-arginine HCl, 0.09% (w/v) L-proline, pH 6.0**				
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**				
Fill Volume		**17.5 mL**				
Storage Condition		**Agitation: Vortex at 1000 rpm at room temperature Freezing/Thawing: Freeze at – 30 °C and thaw at room temperature**				
Assay		**t=0**	**Agitation (minutes)**		**Freezing/Thawing (cycles)**	
			60	**120**	**2**	**4**
	LMW	1.1	1.2	1.1	1.2	1.0
SE-UPLC (%)	Purity	99.0	99.0	99.0	99.0	99.0
	LMW	0.0	0.0	0.0	0.0	0.0
	HMW	1.0	1.0	1.0	1.0	1.0
iCIEF (%)	Region 1C	5.5	5.5	5.1	5.2	5.1
	REGN2810 Main Peak	10.4	10.7	10.6	10.7	10.8
	Region 2C	2.2	1.9	2.1	2.1	2.1
	Region 3C	21.3	21.5	21.6	21.7	21.5
	REGN3767 Main Peak	52.9	53.2	52.9	53.0	53.5
	Region 4C	7.8	7.2	7.6	7.2	7.1
Particulate Analysis by LO (#/container)	≥ 10 µm	143	NR	97	NR	202
	≥ 25 µm	18	NR	0	NR	35
Particulate Analysis by MFI (#/mL)	2µm≤ x <10µm	233	NR	1887	NR	420
	≥ 10 µm	2	NR	12	NR	12
	≥ 25 µm	0	NR	0	NR	4
REGN3767:REGN2810 Molecular Ratio by HIC		4.58	NR	4.57	NR	4.57

Table 11: Research Stability of 400mg:350mg REGN3767-2810 Fixed Dose Combination Drug Product Stored at 5 °C

Formulation	**40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0% (w/v) sucrose, 0.12% (w/v) polysorbate 80, 16.0 mM L-arginine HCl, 0.30% (w/v) L-proline, pH 6.0**										
Container Closure	**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**										
Fill Volume	**10.5 mL**										
Storage Condition	**5 °C**										
Assay	**Length of Storage (months)**										
	t=0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**	**60**
Physical form / Condition	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP	LEF VP			
Clarity	Not > III	Not > III	Not > III	Not > III	Not > IV	Not > III	Not > IV	Not > IV			

Formulation		**40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0% (w/v) sucrose, 0.12% (w/v) polysorbate 80, 16.0 mM L-arginine HCl, 0.30% (w/v) L-proline, pH 6.0**										
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**										
Fill Volume		**10.5 mL**										
Storage Condition		**5 °C**										
Assay		**Length of Storage (months)**										
		t=0	**1**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**	**60**
Color		Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY5	Not > BY6	Not > BY6	Not > BY5			
pH		6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0			
Total Protein (mg/mL)		75.0	75.3	74.1	76.6	73.7	73.7	76.9	80.0			
Potency (%)	REGN3767	100	NR	NR	111	NR	108	NR	70			
	REGN2810	106	NR	NR	109	NR	95	NR	105			
Reduced MCE (%)	Purity	94.4	94.6	94.3	94.4	94.3	93.9	94.6	95.0			
	NGHC	5.1	5.0	5.2	5.3	5.3	5.5	5.0	4.8			
	LMW	0.1	0.1	0.2	0.1	0.2	0.6	0.4	0.0			
Non-reduced MCE (%)	Purity	98.9	98.9	98.7	99.0	98.8	98.5	99.1	99.0			
	LMW	0.9	1.0	1.1	1.0	1.1	1.2	0.8	0.9			
SE-UPLC (%)	Purity	99.2	99.1	99.2	99.1	99.1	99.2	99.2	99.1			
	LMW	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0			
	HMW	0.8	0.8	0.8	0.9	0.8	0.7	0.8	0.9			
Heterodimer by SE-MS (%)		0.05	0.05	0.03	0.05	NR	0.14	0.10	0.18			
iCIEF (%)	Region 1C	13.2	13.0	13.5	14.0	12.5	12.8	12.6	13.4			
	REGN2810 Main Peak	26.6	26.5	26.4	27.5	26.9	26.9	25.7	26.2			
	Region 2C	5.7	4.6	4.7	4.9	4.9	4.7	4.7	4.3			
	Region 3C	13.7	14.3	13.8	13.1	12.4	12.6	15.0	14.5			
	REGN3767 Main Peak	36.2	36.4	35.9	34.8	37.3	36.8	35.2	35.2			
	Region 4C	4.8	5.2	5.6	5.7	6.0	6.3	6.8	6.4			
Particulate Analysis by LO (#/container)	≥ 10 µm	95	NR	67	20	NR	34	NR	34			
	≥ 25 µm	16	NR	7	0	NR	0	NR	0			
Particulate Analysis by MFI (#/mL)	2µm≤ x <10µm	467	NR	1000	1014	NR	837	NR	1268			
	≥ 10 µm	12	NR	14	23	NR	11	NR	15			
	≥ 25 µm	0	NR	2	2	NR	0	NR	2			
Polysorbate 80 (% w/v)		0.11	NR	NR	0.13	NR	0.13	NR	0.13			
REGN3767:REGN2810 Molecular Ratio by HIC		1.13	NR	NR	1.13	NR	1.13	NR	1.14			

Table 12: Research Stability of 400mg:350mg REGN3767-2810 Fixed Dose Combination Drug Product Stored at 25°C/60%RH or 40°C/75% RH

Formulation		**40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0% (w/v) sucrose, 0.12% (w/v) polysorbate 80, 16.0 mM L-arginine HCl, 0.30% (w/v) L-proline, pH 6.0**								
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**								
Fill Volume		**10.5 mL**								
Assay		**t=0**	**Storage at 25 °C/60% RH (months)**				**Storage at 40 °C/75% RH (months)**			
			0.5	**1**	**3**	**6**	**0.25**	**0.5**	**1**	**3**
Physical form / Condition		LEFVP	LEFVP	LEFVP	LEFVP	LEFVP	LEFVP	LEFVP	LEFVP	LEFVP
Clarity		Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III	Not > III
Color		Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6
pH		6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.1
Total Protein (mg/mL)		75.0	76.3	77.0	73.8	74.2	75.1	75.8	75.8	75.5
Potency (%)	REGN3767	100	NR	NR	NR	102	NR	NR	NR	80
	REGN2810	106	NR	NR	NR	76	NR	NR	NR	84
Reduced MCE (%)	Purity	94.4	94.6	94.4	93.4	92.6	94.4	93.7	93.1	90.8
	NGHC	5.1	4.9	5.2	5.5	6.5	5.1	5.7	6.0	7.1
	LMW	0.1	0.2	0.2	0.7	0.9	0.3	0.3	0.5	1.4
Non-reduced MCE (%)	Purity	98.9	98.9	98.7	98.3	98.2	98.6	98.3	97.8	95.7
	LMW	0.9	0.9	1.0	1.4	1.7	1.1	1.3	1.7	3.7
SE-UPLC (%)	Purity	99.2	99.3	99.3	99.1	99.2	99.2	99.0	98.5	96.1
	LMW	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2
	HMW	0.8	0.7	0.7	0.9	0.9	0.8	1.0	1.4	3.8
Heterodimer by SE-MS (%)		0.05	NR	0.07	0.10	0.14	NR	NR	0.14	0.35
iCIEF (%)	Region 1C	13.2	12.5	15.8	16.8	19.7	13.6	16.1	19.2	30.7
	REGN2810 Main Peak	26.6	26.8	24.1	23.6	22.4	25.5	23.7	21.2	11.1
	Region 2C	5.7	4.9	5.9	5.8	4.5	4.8	5.2	4.4	3.0
	Region 3C	13.7	14.0	16.3	16.5	17.6	14.6	16.2	17.7	23.8
	REGN3767 Main Peak	36.2	36.1	31.3	29.7	25.9	33.8	29.6	26.2	17.5
	Region 4C	4.8	5.7	6.7	7.6	9.9	7.9	9.1	11.3	14.0
Particulate Analysis by LO (#/container)	≥ 10µm	95	NR	NR	20	11	NR	NR	NR	37
	≥ 25µm	16	NR	NR	7	0	NR	NR	NR	0
Particulate Analysis by MFI (#/mL)	2µm≤ x <10µm	467	NR	NR	197	639	NR	NR	NR	525
	≥ 10µm	12	NR	NR	2	7	NR	NR	NR	4
	≥ 25µm	0	NR	NR	0	0	NR	NR	NR	4
Polysorbate 80 (% w/v)		0.11	NR	NR	NR	0.13	NR	NR	NR	0.14
REGN3767:REGN2810 Molecular Ratio by HIC		1.13	NR	NR	NR	1.10	NR	NR	NR	1.21

Table 13: Research Stability of 400mg:350mg REGN3767-2810 Fixed Dose Combination Drug Product Effect of Agitation, and Freezing and Thawing

Formulation		**40.0 mg/mL REGN3767, 35.0 mg/mL REGN2810, 10 mM L-histidine, 9.0% (w/v) sucrose, 0.12% (w/v) polysorbate 80, 16.0 mM L-arginine HCl, 0.30% (w/v) L-proline, pH 6.0**				
Container Closure		**20R (20 mL) USP/Ph. Eur. Type 1 borosilicate glass vial; 20mm, grey Flurotec® chlorobutyl stopper; 20 mm Flip-Off ® seal**				
Fill Volume		**10.5 mL**				
Storage Condition		**Agitation: Vortex at 1000 rpm at room temperature Freezing/Thawing: Freeze at – 30 °C and thaw at room temperature**				
Assay		**t=0**	**Agitation (minutes)**		**Freezing/Thawing (cycles)**	
			60	**120**	**2**	**4**
Physical form / Condition		LEFVP	LEFVP	LEFVP	LEFVP	LEFVP
Clarity		Not > III	Not > III	Not > III	Not > III	Not > III
Color		Not > BY6	Not > BY6	Not > BY6	Not > BY6	Not > BY6
pH		6.0	6.0	6.0	6.0	6.0
Total Protein (mg/mL)		75.0	75.0	76.0	75.5	75.2
Potency (%)	REGN3767	100	NR	89	93	NR
	REGN2810	106	NR	75	112	NR
Reduced MCE (%)	Purity	94.4	94.5	94.6	94.5	94.4
	NGHC	5.1	5.0	5.0	5.1	5.1
	LMW	0.1	0.2	0.2	0.1	0.2
Non-reduced MCE (%)	Purity	98.9	98.9	99.0	99.0	98.9
	LMW	0.9	0.9	0.9	0.9	0.9
SE-UPLC (%)	Purity	99.2	99.2	99.2	99.2	99.1
	LMW	0.0	0.0	0.0	0.0	0.0
	HMW	0.8	0.8	0.8	0.8	0.9
iCIEF (%)	Region 1C	13.2	13.0	12.6	13.0	12.7
	REGN2810 Main Peak	26.6	26.3	26.7	26.6	26.5
	Region 2C	5.7	5.0	4.9	4.8	5.4
	Region 3C	13.7	14.6	14.3	14.2	14.5
	REGN3767 Main Peak	36.2	36.0	36.5	36.7	36.1
	Region 4C	4.8	5.0	5.0	4.8	4.8
Particulate Analysis by LO (#/container)	≥ 10µm	95	NR	100	NR	65
	≥ 25µm	16	NR	0	NR	11
Particulate Analysis by MFI (#/mL)	2µm≤ x <10µm	467	NR	536	NR	200
	≥ 10µm	12	NR	7	NR	28
	≥ 25µm	0	NR	0	NR	0
REGN3767:REGN2810 Molecular Ratio by HIC		1.13	NR	1.09	NR	1.09

[0187] Results from this research stability study demonstrate that the 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 FDC DPs are stable for at least

24 months when stored at 2-8 °C. To date, the results from research stability studies indicate that:

- Both FDC DPs are stable when stored at storage condition of 2-8°C for at least 24 months. This supports the recommended long-term storage condition of 2-8°C for the REGN3767-2810 FDC DPs.
- Both FDC DPs are stable when stored at accelerated condition up at 25°C/60% RH up to 1 month.
- Exposure of REGN3767-2810 FDC DPs to temperatures above room temperature should be avoided.
- The main degradation pathways identified for REGN3767-2810 FDC DPs were the formation of HMW species, LMW species, and charge variants.
- Both FDC DPs are stable to interfacial stress (120 minutes vortexing) and up to 4 cycles of freezing (-30°C) and thawing (room temperature).

Example 7: Proven Acceptable Range Stability Study

[0188] This Example summarizes the formulation robustness study for REGN3767-2810 Fixed Dose Combination (FDC) liquid Drug Products (DPs). There are two presentations of the REGN3767-2810 FDC DP (800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810). This formulation robustness study was conducted to assess whether variations in the DP formulation composition for both FDCs, within the defined Proven Acceptable Range (PAR) would significantly affect the long-term stability of 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 DPs.

[0189] During manufacturing of 800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810, variations in the formulation composition may occur. These variations may include the concentration of REGN3767, the concentration of REGN2810, the concentration of the excipients, and/or the pH of the formulation. Because variations in any of these formulation factors could potentially impact the stability of the DP, a formulation robustness study was conducted to assess whether variations in the DP formulation composition, within the defined Proven Acceptable Range (PAR) would significantly affect the long-term stability of REGN3767-2810 FDC DPs.

[0190] DOE Design for PAR study: To evaluate the impact of the individual formulation parameters on long-term storage stability of the REGN3767-2810 FDC DPs

(800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810), a D-optimal multivariate design was applied in the DOE study. The formulation parameters and their ranges examined in this study are summarized in Table 14 and Table 15.

Table 14: Summary of Formulation Parameters and Formulation Ranges for 800mg:175mg REGN3767-2810 DP

Formulation Factor	Nominal Level	Targeted PAR Range	Range Tested
Fill volume	17.5 mL	NA	10.7-17.5 mL
REGN3767 concentration	47.1 mg/mL	42.4-51.8 mg/mL	36.0-51.8 mg/mL
REGN2810 concentration	10.3 mg/mL	9.3-11.3 mg/mL	9.3-38.5 mg/mL
L-histidine concentration	10 mM	8 – 12 mM	8-12 mM
Sucrose concentration	9.7 %	7.8 – 11.6%	7.2 – 11.6%
L-arginine hydrochloride concentration	18.8 mM	15.0-22.6 mM	12.8-22.6 mM
L-proline concentration	0.09 %	0.07 – 0.11%	0.07 – 0.36%
Polysorbate 80 concentration	0.11 %	0.08 – 0.21%	0.08 – 0.22%
pH	6.0	5.7 – 6.3	5.7 – 6.3

Table 15: Summary of Formulation Parameters and Formulation Ranges for 400mg:350mg REGN3767-2810 DP

Formulation Factor	Nominal Level	Targeted PAR Range	Range Tested
Fill volume	10.7 mL	NA	10.7 – 17.5 mL
REGN3767 concentration	40.0 mg/mL	36.0 – 44.0 mg/mL	36.0 – 51.8 mg/mL
REGN2810 concentration	35.0 mg/mL	31.5 – 38.5 mg/mL	9.3 – 38.5 mg/mL
L-histidine concentration	10 mM	8 – 12 mM	8 – 12 mM
Sucrose concentration	9.0 %	7.2 – 10.8%	7.2 – 11.6%
L-arginine hydrochloride concentration	16.0 mM	12.8 – 19.2 mM	12.8 – 22.6 mM
L-proline concentration	0.30 %	0.24 – 0.36%	0.07 – 0.36%
Polysorbate 80 concentration	0.12 %	0.08 – 0.22%	0.08 – 0.22%
pH	6.0	5.7 – 6.3	5.7 – 6.3

[0191] Stability data for the first three months of the formulation robustness study demonstrates that variations in the composition of the REGN3767-REGN2810 formulation within the ranges studied will not adversely impact the stability or quality of both FDCs under the recommended storage condition (2-8 °C). Therefore, the

800mg:175mg REGN3767-2810 and 400mg:350mg REGN3767-2810 FDC DP are considered robust for:

- Fill volume ranging from 10.7 to 17.5 mL;
- REGN3767 concentration ranging from 36.0 mg/mL to 51.8 mg/mL;
- REGN2810 concentration ranging from 9.3 mg/mL to 38.5 mg/mL;
- L-histidine concentration ranging from 8 mM to 12 mM;
- Sucrose concentration ranging from 7.2% to 11.6% (w/v);
- L-arginine hydrochloride concentration ranging from 12.8 mM to 22.6 mM;
- L-proline concentration ranging from 0.07% to 0.36% (w/v);
- Polysorbate 80 concentration ranging from 0.08% to 0.22% (w/v); pH ranging from 5.7 to 6.3.

[0192] The results for long term 2-8 °C storage are shown in **Error! Reference source not found.**. After 12 months of storage at 2-8 °C, varying the formulation compositions within the ranges tested resulted in no meaningful impact to the stability or quality of REGN3767 and REGN2810.

- No precipitate or visible particulate was detected by visual inspection.
- No meaningful changes in total protein recovery (Solo VPE) or molecular ratio (HIC) were observed.
- The pH of the formulations was stable.
- No meaningful increases in subvisible particulates were observed by HIAC and all values were below the acceptable limits set by USP <788>.
- Relative to the control formulations, no meaningful differences were observed in the levels of HMW species as determined by SE-UPLC and LMW species as determined by non-reducing MCE.
- Relative to the control formulations and assay variability, no meaningful differences were observed in the levels of charge variants as determined by iCIEF.
- Relative to the control formulations, no meaningful differences were observed in the levels of heterodimer species as determined by LC-MS.

Overall Summary

[0193] Formulation robustness studies were conducted to evaluate the effect of variations in formulation parameters on the DP formulations subjected to long-term storage, accelerated storage, and agitation conditions. A DOE study demonstrated that variation in the formulation parameters, within the range studied, did not affect the DP quality and stability.

[0194] Specifically, each FDC DP formulation is robust against a ±10% or greater variation in protein concentrations, a ± 25% or greater variation in polysorbate 80 concentration, a ± 20% or greater variation in all other excipient concentrations, and/or a ± 0.3 pH unit variation at target fill volume.

[0195] Overall, the results from the DP robustness studies indicate that variation in the composition of the DP formulation during manufacturing within the ranges studied will not adversely impact the stability or quality of the DP under the recommended storage conditions (2 to 8 °C).

[0196] 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 and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Table 16: Informal Sequence Listing

SEQ ID NO.	Sequence	Description
1	QVQLVESGGG VVQPGRSLRL SCVASGFTFS SYGMHWVRQA PGKGLEWVAI IWYDGSNKYY ADSVKGRFTI SRDNSKNTQY LQMNSLRAED TAVYYCASVA TSGDFDYYGM DVWGQGTTVT VSS	mAb1 HCVR amino acid sequence
2	EIVLTQSPAT LSLSPGERTT LSCRASQRIS TYLAWYQQKP GQAPRLLIYD ASKRATGIPA RFSGSGSGTG FTLTISSLEP EDFAVYYCQQ RSNWPLTFGG GTKVEIK	mAb1 LCVR amino acid sequence
3	GFTFSSYG	mAb1 HCDR1 amino acid sequence
4	IWYDGSNK	mAb1 HCDR2 amino acid sequence
5	ASVATSGDFD YYGMDV	mAb1 HCDR3 amino acid sequence
6	QRISTY	mAb1 LCDR1 amino acid sequence
7	DAS	mAb1 LCDR2 amino acid sequence
8	QQRSNWPLT	mAb1 LCDR3 amino acid sequence
9	QVQLVESGGG VVQPGRSLRL SCVASGFTFS SYGMHWVRQA PGKGLEWVAI IWYDGSNKYY ADSVKGRFTI SRDNSKNTQY LQMNSLRAED TAVYYCASVA TSGDFDYYGM DVWGQGTTVT VSSASTKGPS VFPLAPCSRS TSESTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TKTYTCNVDH KPSNTKVDKR VESKYGPPCP PCPAPPVAGP SVFLFPPKPK DTLMISRTPE VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS	mAb1 heavy chain amino acid sequence

	TYRVVSVLTV LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLGK	
10	EIVLTQSPAT LSLSPGERTT LSCRASQRIS TYLAWYQQKP GQAPRLLIYD ASKRATGIPA RFSGSGSGTG FTLTISSLEP EDFAVYYCQQ RSNWPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	mAb1 light chain amino acid sequence
11	EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSS	mAb2 HCVR amino acid sequence
12	DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFR	mAb2 LCVR amino acid sequence
13	GFTFSNFG	mAb2 HCDR1 amino acid sequence
14	ISGGGRDT	mAb2 HCDR2 amino acid sequence
15	VKWGNIYFDY	mAb2 HCDR3 amino acid sequence
16	LSINTF	mAb2 LCDR1 amino acid sequence
17	AAS	mAb2 LCDR2 amino acid sequence
18	QQSSNTPFT	mAb2 LCDR3 amino acid sequence
19	EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG NIYFDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY	mAb2 heavy chain amino acid sequence

	SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK	
20	DIQMTQSPSS LSASVGDSIT ITCRASLSIN TFLNWYQQKP GKAPNLLIYA ASSLHGGVPS RFSGSGSGTD FTLTIRTLQP EDFATYYCQQ SSNTPFTFGP GTVVDFRRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC	mAb2 light chain amino acid sequence

What is claimed is:

1. A stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) a buffer,

(d) a sugar,

(e) a non-ionic surfactant, and

(f) an amino acid, at pH 6.0 ± 0.3;

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

2. The stable pharmaceutical formulation of claim 1, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from 20 mg/ml to 60 mg/ml.

3. The stable pharmaceutical formulation of claim 1 or 2, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from 35 mg/ml to 52 mg/ml.

4. The stable pharmaceutical formulation of any one of claims 1 to 3, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 40 mg/ml ± 10 mg/ml.

5. The stable pharmaceutical formulation of any one of claims 1 to 3, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of 47.1 mg/ml ± 5 mg/ml.

6. The stable pharmaceutical formulation of any one of claims 1 to 5, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from 5 mg/ml to 50 mg/ml.

7. The stable pharmaceutical formulation of any one of claims 1 to 6, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from 9 mg/ml to 40 mg/ml.

8. The stable pharmaceutical formulation of any one of claims 1 to 7, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 10.3 mg/ml ± 1 mg/ml.

9. The stable pharmaceutical formulation of any one of claims 1 to 7, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of 35 mg/ml ± 4 mg/ml.

10. The stable pharmaceutical formulation of any one of claims 1 to 9, wherein the buffer is selected from phosphate, acetate, and histidine.

11. The stable pharmaceutical formulation of any one of claims 1 to 10, wherein the buffer is histidine.

12. The stable pharmaceutical formulation of any one of claims 1 to 11, wherein the buffer concentration is from 5mM to 20mM.

13. The stable pharmaceutical formulation of any one of claims 1 to 12, wherein the buffer concentration is from 10mM ± 2mM.

14. The stable pharmaceutical formulation of any one of claims 1 to 13, wherein the sugar is sucrose.

15. The stable pharmaceutical formulation of any one of claims 1 to 14, wherein the sugar is present at a concentration of from 5% to 12% w/v.

16. The stable pharmaceutical formulation of any one of claims 1 to 15, wherein the sugar is present at a concentration of 9% ± 2% w/v.

17. The stable pharmaceutical formulation of any one of claims 1 to 16, wherein the non-ionic surfactant is polysorbate.

18. The stable pharmaceutical formulation of any one of claims 1 to 17, wherein the non-ionic surfactant is present at a concentration of from 0.08% to 0.22% w/v.

19. The stable pharmaceutical formulation of any one of claims 1 to 18, wherein the non-ionic surfactant is present at a concentration of 0.1% ± 0.025% w/v.

20. The stable pharmaceutical formulation of any one of claims 1 to 19, wherein the non-ionic surfactant is polysorbate 80 and is present at a concentration of 0.1% ± 0.025% w/v.

21. The stable pharmaceutical formulation of any one of claims 1 to 19, wherein the amino acid is arginine or proline.

22. The stable pharmaceutical formulation of any one of claims 1 to 20, wherein the amino acid is arginine and proline.

23. The stable pharmaceutical formulation of claim 21 or 22, wherein the arginine is present at a concentration of from 12mM to 23mM.

24. The stable pharmaceutical formulation of any one of claims 21 to 23, wherein the arginine is present at a concentration of 16mM ± 4mM.

25. The stable pharmaceutical formulation of any one of claims 21 to 23, wherein the arginine is present at a concentration of 18.8mM ± 4mM.

26. The stable pharmaceutical formulation of any one of claims 21 to 25, wherein the proline is present at a concentration of from 0.07mM to 0.36mM.

27. The stable pharmaceutical formulation of any one of claims 21 to 26, wherein the proline is present at a concentration of 0.09mM ± 0.02mM.

28. The stable pharmaceutical formulation of any one of claims 21 to 25, wherein the proline is present at a concentration of 0.3mM ± 0.06mM.

29. The stable pharmaceutical formulation of any one of claims 1 to 9, further comprising:

(a) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(c) sucrose at a concentration of no more than about 250 mg/ml,

(d) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(e) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(f) proline at a concentration of no more than about 2 mg/ml, and

(i) water for Injection, USP, at pH 6.0 ± 0.3.

30. The stable pharmaceutical formulation of claim 29, comprising:

(a) the buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.25 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.5 mg/ml,

(c) sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml,

(d) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(e) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1.0 mg/ml, and

(f) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.20 mg/ml.

31. The stable pharmaceutical formulation of claim 29 or 30, comprising:

(a) the buffer comprising histidine at a concentration of about 0.74 mg/ml,

(b) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(c) sucrose at a concentration of about 97 mg/ml,

(d) polysorbate 80 at a concentration of about 1.1 mg/ml,

(e) arginine hydrochloride at a concentration of about 4 mg/ml, and

(f) proline at a concentration of about 0.9 mg/ml.

32. A stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.7% ± 2.0% w/v sucrose,

(e) 0.11% ± 0.0275% w/v polysorbate 80,

(f) 18.8mM ± 4mM arginine, and

(g) 0.09% ± 0.02% w/v proline, at pH 6.0 ± 0.3;

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1

comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

33. A stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.0% ± 1.5% w/v sucrose,

(e) 0.12% ± 0.01% w/v polysorbate 80,

(f) 16mM ± 4mM arginine, and

(g) 0.3% ± 0.06% w/v proline, at pH 6.0 ± 0.3;

wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

34. The stable pharmaceutical formulation of any one of claims 1 to 33, wherein the antibodies or antigen-binding fragments thereof are at least 94% pure when stored at 25°C/60% relative humidity for 1 month.

35. The stable pharmaceutical formulation according to any one of the preceding claims, wherein:

the anti-LAG3 antibody HCVR comprises the amino acid sequence of SEQ ID NO: 1 and the LCVR comprises the amino acid sequence of SEQ ID NO: 2.

36. The stable pharmaceutical formulation according to any one of the preceding claims, wherein:

the anti-PD-1 antibody HCVR comprises the amino acid sequence of SEQ ID NO: 11 and the LCVR comprises the amino acid sequence of SEQ ID NO: 12.

37. The stable pharmaceutical formulation according to any one of the preceding claims, wherein:

the anti-LAG3 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.

38. The stable pharmaceutical formulation according to any one of the preceding claims, wherein:

the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

39. The stable pharmaceutical formulation of any one of claims 1 to 38, wherein said formulation is contained in a container.

40. The stable pharmaceutical formulation of claim 39, wherein the container comprises 1600mg of the anti-LAG3 antibody.

41. The stable pharmaceutical formulation of claim 39, wherein the container comprises 400mg of the anti-LAG3 antibody.

42. The stable pharmaceutical formulation of any one of claims 39 to 41, wherein the container comprises 350mg of the anti-PD-1 antibody.

43. The stable pharmaceutical formulation of any one of claims 39 to 42, wherein the container is a vial.

44. The stable pharmaceutical formulation of claim 43, wherein the vial is a 10 mL or 20 ml Type 1 clear glass vial.

45. The stable pharmaceutical formulation of any one of claims 39 to 42, wherein the container is a syringe.

46. The stable pharmaceutical formulation of claim 45, wherein the syringe is low-tungsten glass.

47. The stable pharmaceutical formulation of any one of claims 39 to 42, wherein the container is a prefilled syringe.

48. The stable pharmaceutical formulation of any one of claims 39 to 42, contained in an autoinjector.

49. A kit comprising the pharmaceutical formulation of any one of claims 1 to 38, a container, and instructions.

50. The kit of claim 49 wherein the container is a glass vial.

51. The kit of claim 49, wherein the container is a prefilled syringe.

52. The kit of claim 49, wherein the container is an autoinjector.

53. A pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof,

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof,

(c) 10mM ± 2mM histidine,

(d) 9.0% ± 2.0% w/v sucrose,

(e) 0.12% ± 0.03% w/v polysorbate 80,

(f) 16mM ± 4mM arginine, and

(g) 0.3% ± 0.06% w/v or 0.09% ± 0.02% w/v proline, at pH 6.0 ± 0.3;

for use in a method of treating cancer or inhibiting the growth of a tumor in a subject in need thereof, wherein:

the anti-LAG3 antibody or antigen-binding fragment thereof comprises: three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of a heavy chain variable region (HCVR) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of a light chain variable region (LCVR), wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8, and

the anti-PD-1 antibody or antigen-binding fragment thereof comprises: three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18.

54. The pharmaceutical formulation for use according to claim 53, wherein the pharmaceutical formulation is administered intravenously, subcutaneously, or intraperitoneally.

55. The pharmaceutical formulation for use according to claim 53 or 54, wherein the cancer is selected from the group consisting of astrocytoma, bladder cancer, blood cancer, bone cancer, brain cancer, breast cancer, cervical cancer, clear cell renal cell carcinoma, colorectal cancer, microsatellite-intermediate colorectal cancer, cutaneous squamous cell carcinoma, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, fibrosarcoma, gastric cancer, glioblastoma, glioblastoma multiforme, head and neck squamous cell carcinoma, hepatic cell carcinoma, leukemia, liver cancer, leiomyosarcoma, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, nasopharyngeal cancer, non-small cell lung cancer, osteosarcoma, ovarian cancer, pancreatic cancer, primary and/or recurrent cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, squamous cell cancer, synovial sarcoma, thyroid cancer, triple negative breast cancer, uterine cancer, and Wilms' tumor.

56. The pharmaceutical formulation for use according to any one of claims 53 to 55, wherein:

the anti-LAG3 antibody HCVR comprises the amino acid sequence of SEQ ID NO: 1 and the LCVR comprises the amino acid sequence of SEQ ID NO: 2.

57. The pharmaceutical formulation for use according to any one of claims 53 to 56, wherein:

the anti-PD-1 antibody HCVR comprises the amino acid sequence of SEQ ID NO: 11 and the LCVR comprises the amino acid sequence of SEQ ID NO: 12.

58. The pharmaceutical formulation for use according to any one of claims 53 to 57, wherein:

the anti-LAG3 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.

59. The pharmaceutical formulation for use according to any one of claims 53 to 58, wherein:

the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

60. A stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of an HCVR, and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8;

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18,

(c) a buffer comprising histidine at a concentration of no more than about 2 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of no more than about 5 mg/ml,

(e) sucrose at a concentration of no more than about 250 mg/ml,

(f) polysorbate 80 at a concentration of no more than about 5 mg/ml,

(g) arginine hydrochloride at a concentration of no more than about 10 mg/ml,

(h) proline at a concentration of no more than about 2 mg/ml, and

(i) water for Injection, USP, at pH 6.0 ± 0.3,

wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 10 mg/ml to about 100 mg/ml, and the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 5 mg/ml to about 50 mg/ml.

61. The stable pharmaceutical formulation of claim 60, wherein the anti-LAG3 antibody comprises the HCVR comprising the amino acid sequence of SEQ ID NO: 1 and the LCVR comprises the amino acid sequence of SEQ ID NO: 2.

62. The stable pharmaceutical formulation according to claim 60 or 61, wherein the anti-LAG3 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.

63. The stable pharmaceutical formulation according to any one of claims 60 to 62, wherein the anti-PD-1 antibody comprises the HCVR comprising the amino acid sequence of SEQ ID NO: 11 and the LCVR comprising the amino acid sequence of SEQ ID NO: 12.

64. The stable pharmaceutical formulation according to any one of claims 60 to 63, wherein the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

65. The stable pharmaceutical formulation of any one of claims 60 to 64, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 20 mg/ml to about 75 mg/ml.

66. The stable pharmaceutical formulation of any one of claims 60 to 65, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 25 mg/ml to about 60 mg/ml.

67. The stable pharmaceutical formulation of any one of claims 60 to 66, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 35 mg/ml to about 55 mg/ml.

68. The stable pharmaceutical formulation of any one of claims 60 to 67, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of from about 40 mg/ml to about 50 mg/ml.

69. The stable pharmaceutical formulation of any one of claims 60 to 68, wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of about 47 mg/ml.

70. The stable pharmaceutical formulation of any one of claims 60 to 69, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 8 mg/ml to about 25 mg/ml.

71. The stable pharmaceutical formulation of any one of claims 60 to 70, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of from about 10 mg/ml to about 15 mg/ml.

72. The stable pharmaceutical formulation of any one of claims 60 to 71, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of about 10 mg/ml.

73. The stable pharmaceutical formulation of any one of claims 60 to 72, comprising:

(c) the buffer comprising histidine at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.20 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of from 1 ± 0.2 mg/ml to 2 ± 0.4 mg/ml,

(e) sucrose at a concentration of from 50 ± 10 mg/ml to 100 ± 20 mg/ml,

(f) polysorbate 80 at a concentration of from 1 ± 0.25 mg/ml to 2 ± 0.5 mg/ml,

(g) arginine hydrochloride at a concentration of from 2 ± 0.4 mg/ml to 5 ± 1.0 mg/ml, and

(h) proline at a concentration of from 0.5 ± 0.1 mg/ml to 1 ± 0.2 mg/ml.

74. The stable pharmaceutical formulation of any one of claims 60 to 73, comprising:

(c) the buffer comprising histidine at a concentration of about 0.74 mg/ml,

(d) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(e) sucrose at a concentration of about 97 mg/ml,

(f) polysorbate 80 at a concentration of about 1.1 mg/ml,

(g) arginine hydrochloride at a concentration of about 4 mg/ml, and

(h) proline at a concentration of about 0.9 mg/ml.

75. The stable pharmaceutical formulation of any one of claims 60 to 74, wherein the antibodies or antigen-binding fragments thereof are at least 94% pure when stored at 25°C/60% relative humidity for 1 month.

76. The stable pharmaceutical formulation of any one of claims 60 to 75, wherein said formulation is contained in a container.

77. The stable pharmaceutical formulation of claim 76, wherein the container comprises 800 mg of the anti-LAG3 antibody.

78. The stable pharmaceutical formulation of claim 76 or 77, wherein the container comprises 175 mg of the anti-PD-1 antibody.

79. The stable pharmaceutical formulation of any one of claims 76 to 78, wherein the container is a vial.

80. The stable pharmaceutical formulation of claim 79, wherein the vial is a 10 mL or 20 ml Type 1 clear glass vial.

81. The stable pharmaceutical formulation of any one of claims 76 to 78, wherein the container is a syringe.

82. The stable pharmaceutical formulation of claim 81, wherein the syringe is low-tungsten glass.

83. The stable pharmaceutical formulation of any one of claims 76 to 78, wherein the container is a prefilled syringe.

84. The stable pharmaceutical formulation of any one of claims 76 to 78, contained in an autoinjector.

85. A stable pharmaceutical formulation comprising:

(a) anti-human lymphocyte activation gene-3 antibody (anti-LAG3 antibody) or antigen-binding fragment thereof comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) of an HCVR, and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8;

(b) anti-human programmed death 1 antibody (anti-PD-1 antibody) or antigen-binding fragment thereof comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) of an HCVR and three light chain CDRs (LCDR1, LCDR2 and LCDR3) of an LCVR, wherein HCDR1 comprises the amino acid sequence of SEQ ID NO: 13; HCDR2 comprises the amino acid sequence of SEQ ID NO: 14; HCDR3 comprises the amino acid sequence of SEQ ID NO: 15; LCDR1 comprises the amino acid sequence of SEQ ID NO: 16; LCDR2 comprises the amino acid sequence of SEQ ID NO: 17; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 18,

(c) a buffer comprising histidine at a concentration of about 0.74 mg/ml,

(d) sucrose at a concentration of about 97 mg/ml,

(e) L-histidine hydrochloride monohydrate at a concentration of about 1.1 mg/ml,

(f) arginine hydrochloride at a concentration of about 4 mg/ml,

(g) proline at a concentration of about 0.9 mg/ml,

(h) polysorbate 80 at a concentration of about 1.1 mg/ml; and

(i) water for Injection, USP, at pH 6.0 ± 0.3;

wherein the anti-LAG3 antibody or antigen-binding fragment thereof is present at a concentration of about 47 mg/ml, and the anti-PD-1 antibody or antigen-binding fragment thereof is present at a concentration of about 10 mg/ml.

86. A kit comprising the pharmaceutical formulation of any one of claims 60 to 74 and 85, a container, and instructions.

87. The kit of claim 86, wherein the container is a glass vial.

88. The kit of claim 86, wherein the container is a prefilled syringe.

89. The kit of claim 86, wherein the container is an autoinjector.

90. The pharmaceutical formulation of any one of claims 60 to 74 and 85 for use in a method of treating cancer or inhibiting the growth of a tumor in a subject in need thereof.

91. The pharmaceutical formulation for use according to claim 90, wherein the pharmaceutical formulation is administered intravenously, subcutaneously, or intraperitoneally.

92. The pharmaceutical formulation for use according to claim 90 or 91, wherein the cancer is selected from the group consisting of astrocytoma, bladder cancer, blood cancer, bone cancer, brain cancer, breast cancer, cervical cancer, clear cell renal cell carcinoma, colorectal cancer, microsatellite-intermediate colorectal cancer, cutaneous squamous cell carcinoma, diffuse large B-cell lymphoma, endometrial cancer, esophageal cancer, fibrosarcoma, gastric cancer, glioblastoma, glioblastoma multiforme, head and neck squamous cell carcinoma, hepatic cell carcinoma, leukemia, liver cancer, leiomyosarcoma, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, nasopharyngeal cancer, non-small cell lung cancer, osteosarcoma, ovarian cancer, pancreatic cancer, primary and/or recurrent cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, squamous cell cancer, synovial sarcoma, thyroid cancer, triple negative breast cancer, uterine cancer, and Wilms' tumor.