

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an antibody or antigen binding fragment that binds to tumor necrosis factor-like protein 1A (anti-TL1A antibody or antigen binding fragment) at a concentration of (i) about 150 mg/mL to about 250 mg/mL; (ii) about 175 mg/mL to about 225 mg/mL; (iii) greater than about 150, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, or 225 mg/mL; or (iv) about 150, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, or 225 mg/mL.
2. The composition of claim 1, wherein:
 - (i) the composition has a total volume of about 0.5 mL to about 1.5 mL;
 - (ii) the composition has a viscosity of less than about 20 cP; or
 - (iii) the composition has a percentage aggregation of anti-TL1A antibody or antigen binding fragment as measured by size exclusion chromatography of less than about 2% of the total anti-TL1A antibody or antigen binding fragment in the composition.
3. The composition of claim 1 or 2, further comprising:
 - (i) a surfactant;
 - (ii) a salt;
 - (iii) a stabilizer;
 - (iv) a buffering agent such that the composition has a pH of about 4.5 to about 8.0; or
 - (v) a combination of any of (i) to (iv).
4. The composition of claim 3, wherein:
 - (i) the surfactant comprises a nonionic surfactant;
 - (ii) the surfactant comprises polysorbate-20;
 - (iii) the surfactant is present at a concentration of about 0.005% to about 0.05% (v/v) of the composition;
 - (iv) the surfactant is present at a concentration of about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.011%, about 0.012%, about 0.013%, about 0.014%, about 0.015%, about 0.016%, about 0.017%, about 0.018%, about 0.019%, about 0.02%, about 0.021%, about 0.022%, about 0.023%, about

0.024%, about 0.025%, about 0.026%, about 0.027%, about 0.028%, about 0.029%, or about 0.03% (v/v) of the composition;

(v) the salt comprises sodium chloride, glycine, lysine-hydrochloride, arginine-hydrochloride, arginine glutamate, potassium chloride, magnesium chloride, or calcium chloride, or a combination thereof;

(vi) the salt comprises sodium chloride;

(vii) the salt is present at a concentration of about 10 mM to about 100 mM in the composition;

(viii) the salt is present at a concentration of about 40 mM in the composition;

(ix) the stabilizer comprises a sugar, polyol, amino acid, or polymer, cyclodextrin (e.g., HP-b-CD), or a combination thereof;

(x) the stabilizer comprises the sugar, wherein optionally the sugar comprises sucrose, glucose, trehalose, maltose, or lactose, or a combination thereof;

(xi) the stabilizer comprises sucrose;

(xii) the stabilizer is present at a concentration of about 50 mM to about 300 mM in the composition

(xiii) the stabilizer is present at a concentration of about 150 mM, about 160 mM, about 170 mM, about 180 mM, about 190 mM, about 200 mM, about 210 mM, about 220 mM, about 230 mM, about 240 mM, or about 250 mM

(xiv) the buffering agent comprises acetate, phosphate, citrate, glutamate, succinate, gluconate, histidine, glycylglycine, citric acid, Tris (tris (hydroxymethyl) aminomethane), or diethanolamine, or a combination thereof;

(xv) the buffering agent comprises acetate;

(xvi) the buffering agent is present at a concentration of about 10 mM to about 50 mM in the composition;

(xvii) the composition comprises about 20 mM buffer;

(xviii) the composition has a pH of about 4.5 to about 7.5, wherein optionally the composition has a pH of about 5 to about 5.5;

(xix) the composition has a pH of about 5.3;

(xx) any combination of (i) to (xix); or

(xxi) the composition comprises 20 mM sodium acetate, 220 mM sucrose, 40 mM NaCl, and 0.02% polysorbate-20, at pH 5.3.

5. Use of an antibody or antigen binding fragment that binds to tumor necrosis factor-like protein 1A (anti-TL1A antibody or antigen binding fragment) in the manufacture of a medicament for the treatment of an inflammatory disease in a subject, wherein (i) the anti-TL1A antibody or antigen binding fragment is to be administered to the subject at a first dose up to about 1000 mg; (ii) the first dose is to be administered to the subject at a first time point, and a second dose is to be administered to the subject at a second time point and; and (iii) the second time point is about 1, 2, 3, or 4 weeks after the first time point, wherein the second dose comprises about 150 mg to about 600 mg.

6. The use of claim 5, wherein:

(i) a third dose of anti-TL1A antibody or antigen binding fragment is to be administered to the subject at a third time point, wherein the third time point is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 days after the second time point and the third dose comprises about 150 mg to about 600 mg; and/or

(ii) an additional dose of the anti-TL1A antibody or antigen binding fragment is to be administered to the subject at one or more additional time points, wherein optionally the one or more additional time points comprises about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 additional time points, wherein each additional time point is independently about 1, 2, 3, or 4 weeks after a previous time point and the additional dose comprises from about 150 mg to about 1000 mg anti-TL1A.

7. Use of an anti-TL1A antibody or antigen binding fragment in the manufacture of a medicament for treating IBD in a subject in need thereof,

wherein the anti-TL1A antibody or antigen binding fragment is to be used at an effective dose such that the concentration of TL1A in a diseased tissue in the subject after the use is below the concentration of TL1A in a corresponding tissue in a control subject without IBD,

wherein optionally the diseased tissue in the subject produces up to 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, or more fold of TL1A compared to the corresponding tissue in the control subject during the induction regimen.

8. The use of claim 7, wherein:

(i) the effective dose comprises an induction regimen; or

(ii) the effective dose comprises an induction regimen and a

maintenance regimen after the induction regimen, wherein the TL1A in the diseased tissue in the subject is maintained with the maintenance regimen of the anti-TL1A antibody or antigen binding fragment.

9. The use of claim 8, wherein:

(i) the induction regimen comprises a one-time administration of the anti-TL1A antibody or antigen binding fragment, wherein optionally the anti-TL1A antibody or antigen binding fragment is to be administered at 200 mg/dose, 250 mg/dose, 300 mg/dose, 350 mg/dose, 400 mg/dose, 450 mg/dose, 500 mg/dose, 550 mg/dose, 600 mg/dose, 650 mg/dose, 700 mg/dose, 750 mg/dose, 800 mg/dose, 850 mg/dose, 900 mg/dose, 950 mg/dose, 1000 mg/dose, 1100 mg/dose, 1200 mg/dose, 1250 mg/dose, 1300 mg/dose, 1400 mg/dose, 1500 mg/dose, 1600 mg/dose, 1700 mg/dose, 1750 mg/dose, 1800 mg/dose, 1900 mg/dose, or 2000 mg/dose;

(ii) the induction regimen comprises multiple administrations of the anti-TL1A antibody or antigen binding fragment, wherein optionally the induction regimen comprises administrations of (1) 1000 mg/dose on week 0, 1000 mg/dose on week 2, 1000 mg/dose on week 6, and 1000 mg/dose on week 10; (2) 500 mg/dose on week 0, 500 mg/dose on week 2, 500 mg/dose on week 6, and 500 mg/dose on week 10; (3) 1000 mg/dose on week 0, 1000 mg/dose on week 2, 1000 mg/dose on week 6, and 500 mg/dose on week 10; (4) 1000 mg/dose on week 0, 1000 mg/dose on week 2, 500 mg/dose on week 6, and 500 mg/dose on week 10; or (5) 1000 mg/dose on week 0, 500 mg/dose on week 2, 500 mg/dose on week 6, and 500 mg/dose on week 10; or

(iii) the induction regimen comprises administration of 2000, 1950, 1900, 1850, 1800, 1750, 1700, 1650, 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, or 200 mg/dose, wherein optionally the induction regimen comprises administration once every 2, 4, 6, or 8 weeks or the induction regimen comprises administration once every 2 or 4 weeks for the first 2 administrations and then once every 2, 4, 6, or 8 weeks for the remaining induction regimen.

10. The use of claim 8 or 9, wherein:

(i) the maintenance regimen comprises multiple administrations of the anti-TL1A antibody or antigen binding fragment;

(ii) the maintenance regimen comprises administrations of the anti-

TL1A antibody or antigen binding fragment at (1) 500 mg/dose every 4 weeks, (2) 400 mg/dose every 4 weeks, (3) 300 mg/dose every 4 weeks, (4) 250 mg/dose every 4 weeks, (5) 200 mg/dose every 4 weeks, (6) 150 mg/dose every 4 weeks, (7) 100 mg/dose every 4 weeks, (8) 50 mg/dose every 4 weeks, (9) 500 mg/dose every 6 weeks, (10) 400 mg/dose every 6 weeks, (11) 300 mg/dose every 6 weeks, (12) 250 mg/dose every 6 weeks, (13) 200 mg/dose every 6 weeks, (14) 150 mg/dose every 6 weeks, (15) 100 mg/dose every 6 weeks, (16) 50 mg/dose every 6 weeks, (17) 500 mg/dose every 8 weeks, (18) 400 mg/dose every 8 weeks, (19) 300 mg/dose every 8 weeks, (20) 250 mg/dose every 8 weeks, (21) 200 mg/dose every 8 weeks, (22) 150 mg/dose every 8 weeks, (23) 100 mg/dose every 8 weeks, or (24) 50 mg/dose every 8 weeks;

(iii) the maintenance regimen comprises administration of the anti-TL1A antibody or antigen binding fragment at 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, or 50 mg/dose;

(iv) the maintenance regimen comprises administration of the anti-TL1A antibody or antigen binding fragment once every 2, 4, 6, 8, 10, or 12 weeks;

(v) the maintenance regimen comprises administrations of the anti-TL1A antibody or antigen binding fragment at 250 mg/dose every 4 weeks; or

(vi) the maintenance regimen continues for 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 44, 48, or 52 weeks.

11. The use of any one of claims 7 to 10, wherein:

(i) binding affinity of the antibody or antigen binding fragment to monomeric TL1A as measured by dissociation equilibrium constant ($K_{D\text{-monomer}}$) is comparable to binding affinity of the antibody or antigen binding fragment to trimeric TL1A as measured by dissociation equilibrium constant ($K_{D\text{-trimer}}$), wherein optionally the $K_{D\text{-monomer}}$ is within 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold of the $K_{D\text{-trimer}}$, and wherein optionally the $K_{D\text{-monomer}}$ is no more than 0.06 nM and the $K_{D\text{-trimer}}$ is no more than 0.06 nM;

(ii) the IBD is Crohn's disease or ulcerative colitis; or

(iii) the diseased tissue comprises any one or more selected from the group consisting of colon, small intestine, rectum, cecum, ileum, spleen, a fibrotic tissue from IBD, other tissues with IBD pathology, and other tissues of IBD pathogenesis.

12. The use of any one of claims 8 to 11, wherein:

(1) the effective dose or the induction regimen is determined by a dose

determination method, wherein the dose determination method comprises: (i) receiving a parameter of TL1A over-production in the diseased tissue comparing to TL1A production in a normal reference tissue; (ii) integrating the parameters received in (a) to an integrated whole-body physiologically based pharmacokinetic (PBPK) model or a population pharmacokinetic model (popPK); and (iii) determining the effective dose or the induction regimen such that the concentration of TL1A in diseased tissue in the subject after the use is below the concentration of TL1A in a corresponding tissue in a control subject without IBD; and/or

(2) the maintenance regimen is determined by a dose determination method, wherein the dose determination method comprises: (i) receiving a parameter of TL1A over-production in the diseased tissue comparing to TL1A production in a normal reference tissue; (ii) integrating the parameter received in (i) to an integrated whole-body physiologically based pharmacokinetic (PBPK) model or a population pharmacokinetic model (popPK); and (iii) determining the maintenance regimen such that the concentration of TL1A in diseased tissue in the subject after step (c) is below the concentration of TL1A in a corresponding tissue in a control subject without IBD.

13. The composition of any one of claims 1 to 4, or the use of any one of claims 5 to 12, wherein the anti-TL1A antibody or antigen binding fragment comprises a heavy chain variable region comprising: an HCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 1, an HCDR2 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 2-5, and an HCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 6-9; and a light chain variable region comprising an LCDR1 comprising an amino acid sequence set forth by SEQ ID NO: 10, an LCDR2 comprising an amino acid sequence set forth by SEQ ID NO: 11, an LCDR3 comprising an amino acid sequence set forth by any one of SEQ ID NOS: 12-15.

14. The composition of any one of claims 1 to 4, or the use of any one of claims 5 to 12, wherein:

(i) the anti-TL1A antibody or antigen binding fragment comprises a heavy chain variable framework region comprising a human IGHV1-46*02 framework or a modified human IGHV1-46*02 framework, and a light chain variable framework region comprising a human IGKV3-20 framework or a modified human IGKV3-20 framework; wherein the heavy chain variable framework region and the light chain variable framework

region collectively comprise no or fewer than nine amino acid modification(s) from the human IGHV1-46*02 framework and the human IGKV3-20 framework; or

(ii) the anti-TL1A antibody or antigen binding fragment comprises a heavy chain variable domain comprising an amino acid sequence at least 97% identical to any one of SEQ ID NOS: 101-169, and a light chain variable domain comprising an amino acid sequence at least 97% identical to any one of SEQ ID NOS: 201-220.

15. The composition of any one of claims 1 to 4, or the use of any one of claims 5 to 12, wherein the anti-TL1A antibody or antigen binding fragment comprises a heavy chain variable region comprising SEQ ID NO: 301

X1VQLVQSGAEVKKPGASVKVSCKAS[HCDR1]WVX2QX3PGQGLEWX4G[HCDR2]
RX5TX6TX7DTSTSTX8YX9ELSSLRSEDFAVYYCAR[HCDR3]WGQGTTVTVSS, and a light chain variable region comprising SEQ ID NO: 303

EIVLTQSPGTLSPGERATLSC[LCDR1]WYQQKPGQAPRX10X11Y[LCDR2]GIPDR
FSGSGSGTDFLTISRLEPEDFAVYYC[LCDR3]FGGGTKLEIK, wherein each of X1-X11 is independently selected from A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V, wherein HCDR1 comprises an amino acid sequence set forth by SEQ ID NO: 1, HCDR2 comprises an amino acid sequence set forth by any one of SEQ ID NOS: 2-5, HCDR3 comprises an amino acid sequence set forth by any one of SEQ ID NOS: 6-9, LCDR1 comprises an amino acid sequence set forth by SEQ ID NO: 10, LCDR2 comprises an amino acid sequence set forth by SEQ ID NO: 11, and LCDR3 comprises an amino acid sequence set forth by any one of SEQ ID NOS: 12 or 13.

16. An antibody or antigen binding fragment that binds to tumor necrosis factor-like protein 1A (anti-TL1A antibody or antigen binding fragment) for use in therapy.