

SUMMARY

[0007] Provided in accordance with the present disclosure is disclosure for the first time demonstrating that the addition of an amino acid aggregation inhibitor to an aqueous solution comprising a high concentration of an anti-RANKL antibody leads to a reduced amount of antibody aggregates formed over time, as well a slower formation rate of such aggregates. The present disclosure also provides for a pH effect on aggregate formation in concentrated aqueous solutions of anti-RANKL antibody, wherein decreased aggregate formation is observed when the pH of the aqueous solutions is in the range of about 5.0 to less than 5.2. Further suggested by the disclosure presented herein is that the stabilization of the anti-RANKL antibody occurs through interactions between the amino acid aggregation inhibitor and the antibody. Without being bound to any particular theory, it is contemplated that hydrophobic interactions, as well as other types of intermolecular interactions, between the amino acid aggregation inhibitor and the anti-RANKL antibody have a stabilizing effect on the concentrated antibody solutions. Accordingly, the disclosure of the present disclosure relates to stable aqueous pharmaceutical formulations comprising a high concentration of an anti-RANKL antibody which formulations comprise low amounts (e.g., less than about 2%) of aggregates.

[0007a] In one aspect, the present disclosure refers to an aqueous pharmaceutical formulation comprising (i) a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody, or an antigen-binding portion thereof wherein the aqueous pharmaceutical formulation (A) further comprises an amino acid aggregation inhibitor, (B) has a pH in a range of about 5.0 to less than 5.2 and has a concentration of the anti-RANKL monoclonal antibody, or an antigen-binding portion thereof, greater than 70 mg/mL, or (C) both (A) and (B), optionally, further comprising an amino acid aggregation inhibitor comprising an aromatic amino acid, such as phenylalanine and tryptophan.

[0007b] In another aspect, the present disclosure refers to a container, optionally, a vial, pre-filled syringe (PFS), or glass container containing an aqueous pharmaceutical formulation of any one of the preceding claims, optionally, containing about 1 mL or less of the formulation, optionally, about 0.5 mL.

[0007c] In another aspect, the present disclosure refers to a formulation comprising denosumab at a concentration of about 108 mg/mL to about 132 mg/mL, about 28.8 mM to about 35.2 mM acetate, 33.3 mM to about 40.7 mM phenylalanine, 3.51% (w/v) to about 4.29% (w/v) sorbitol, and about 0.009% (w/v) to about 0.011% (w/v) polysorbate 20, at pH 5.1.

[0007d] In another aspect, the present disclosure refers to an aqueous pharmaceutical formulation as described herein, container as described herein or formulation as described herein for use in therapy.

[0007e] In another aspect, the present disclosure refers to the use of an aqueous pharmaceutical formulation as described herein, container as described herein or formulation as described herein in the manufacture of a medicament for (a) treatment or prevention of an SRE in a subject with bone metastases from solid tumors, (b) treatment or prevention of an SRE in a subject who is an adult or a skeletally mature adolescent with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, (c) treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy in a subject, (d) treatment or prevention of an SRE in a subject with multiple myeloma or with bone metastases from a solid tumor, (e) treatment of osteoporosis of postmenopausal women at high risk for fracture, (f) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, (g) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, (h) treatment to increase bone mass in men with osteoporosis at high risk for fracture, (i) therapy with calcium or vitamin D, (j) treating giant cell tumor of bone in a patient in need thereof, (k) treating hypercalcemia of malignancy in a patient in need thereof, (l) treating osteoporosis in a patient in need thereof, (m) increasing bone mass in a patient in need thereof.

[0008] Accordingly, one example of the disclosure is an aqueous pharmaceutical formulation comprising a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof at a concentration of greater than 70 mg/mL and having a pH in a range of about 5.0 to less than 5.2.

[0009] Another example of the disclosure is an aqueous pharmaceutical formulation comprising a mixture of a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof and an amino acid

aggregation inhibitor. In exemplary examples, the amino acid aggregation inhibitor comprises an amino acid comprising a charged side chain, an aromatic amino acid, or a hydrophobic amino acid. In exemplary instances, the amino acid comprising a charged side chain is an amino acid comprising a positive-charged side chain, such as, for example, arginine and lysine. In exemplary examples, the aromatic amino acid comprises a phenyl or an indole. Optionally, the aromatic amino acid further comprises a C₁-C₆ alkyl chain between the alpha carbon and the phenyl or indole. Amino acids, including, for instance, phenylalanine and tryptophan, are exemplary amino acid aggregation inhibitors. In exemplary instances, the amino acid aggregation inhibitor is a hydrophobic amino acid having a score greater than about 2.5 on the Kyte and Doolittle hydrophobicity scale. Optionally, the hydrophobic amino acid is valine, leucine or isoleucine. Additional amino acid aggregation inhibitors are contemplated as described herein.

[0010] In exemplary instances, the aqueous pharmaceutical formulation further comprises a tonicity modifier, a surfactant, a buffer, or any combination thereof.

[0011] Another example of the disclosure is a presentation of the formulation for storage or use, e.g. in a single-use vial, single-use syringe, or glass, glass-lined, or glass-coated primary container. An exemplary example of the disclosure is a container, optionally, a vial, pre-filled syringe (PFS), or glass container comprising any of the aqueous pharmaceutical formulations described herein. The container, in exemplary instances, comprises about 1 mL or less (e.g., about 0.5 mL) of the aqueous pharmaceutical formulation.

[0012] Another example of the disclosure provides methods of making a stable, aqueous pharmaceutical formulation comprising a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody, or an antigen-binding portion thereof, comprising combining the anti-RANKL monoclonal antibody, or antigen-binding portion thereof, at a concentration greater than 70 mg/mL with an amino acid aggregation inhibitor, a buffer, a surfactant, and optionally, a tonicity modifier. Examples of the disclosure include the stable, aqueous pharmaceutical formulation made according to any one of the methods of making a stable, aqueous pharmaceutical formulation described herein.

[0013] Another example of the disclosure provides methods of using a formulation as described herein for preventing or treating a disease responsive to a human anti-RANKL

monoclonal antibody or an antigen-binding portion thereof. In exemplary examples, the use encompasses therapeutic treatment of a subject encompassing treatment or prevention of a skeletal-related event (SRE), treatment or prevention of a giant cell tumor of bone, treatment or prevention of hypercalcemia of malignancy, treatment or prevention of osteoporosis, or increasing bone mass, in a subject. For instance, the therapeutic treatment encompasses (a) treatment or prevention of an SRE in a subject with bone metastases from solid tumors, (b) treatment or prevention of an SRE in a subject who is an adult or a skeletally mature adolescent with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, (c) treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy in a subject, (d) treatment or prevention of an SRE in a subject with multiple myeloma or with bone metastases from a solid tumor, (e) treatment of osteoporosis of postmenopausal women at high risk for fracture, (f) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, (g) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, (h) treatment to increase bone mass in men with osteoporosis at high risk for fracture, (i) therapy with calcium or vitamin D.

[0014] Additional examples of the disclosure include a method of preventing a skeletal-related event (SRE) in a patient in need thereof, a method of treating giant cell tumor of bone in a patient in need thereof, a method of treating hypercalcemia of malignancy in a patient in need thereof, a method of treating osteoporosis in a patient in need thereof, and a method of increasing bone mass in a patient in need thereof. The methods comprise administering to the patient an effective amount of any one of the formulations described herein. In exemplary instances, the formulation is subcutaneously delivered to the patient.

[0015] Another example of the disclosure provides the use of denosumab, or another human anti-RANKL monoclonal antibody or an antigen-binding portion thereof, in the manufacture of a medicament as described herein for treating a patient in need of a human anti-RANKL monoclonal antibody.

[0016] Another example of the disclosure is a kit including a composition or article described herein together with a package insert, package label, instructions, or other labeling directing or disclosing any of the methods or embodiments disclosed herein.

[0017] Another example of the disclosure is a method of improving the stability of an aqueous pharmaceutical formulation including a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof, at a concentration of greater than 70 mg/mL, including the step of preparing the aqueous pharmaceutical formulation including the human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof at a pH in a range of about 5.0 to less than 5.2, wherein the aqueous pharmaceutical formulation demonstrates improved stability at the pH in a range of about 5.0 to less than 5.2 compared to an equivalent aqueous pharmaceutical formulation that is not at a pH in a range of about 5.0 to less than 5.2.

[0018] Another example of the disclosure is a method of improving the stability of an aqueous pharmaceutical formulation including a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof, including the step of preparing the aqueous pharmaceutical formulation comprising the human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody or an antigen-binding portion thereof in admixture with an amino acid aggregation inhibitor, wherein the aqueous pharmaceutical formulation demonstrates improved stability with the amino acid aggregation inhibitor compared to an equivalent aqueous pharmaceutical formulation without the amino acid aggregation inhibitor.

[0019] Another example of the disclosure is a method of reducing the level of HMWS aggregates in a solution of denosumab or another human anti-RANKL monoclonal antibody.

[0020] Further examples and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compositions, articles, and methods are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the disclosure to the specific embodiments described herein. For the compositions, articles, and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various examples provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Figures 1, 2, and 8 show the percent HMWS monitored by SE-UHPLC as a function of formulation and time at 37 °C for various high-concentration denosumab formulations. The legend of Figure 1 accords to the formulation having the Abbreviation shown in Table 1. The legend of Figure 8 accords to the letter shown in Table 5.

What is claimed is:

1. An aqueous pharmaceutical formulation comprising (i) a human anti-human receptor activator of nuclear factor kappa-B ligand (anti-RANKL) monoclonal antibody, or an antigen-binding portion thereof wherein the aqueous pharmaceutical formulation (A) further comprises an amino acid aggregation inhibitor, (B) has a pH in a range of about 5.0 to less than 5.2 and has a concentration of the anti-RANKL monoclonal antibody, or an antigen-binding portion thereof, greater than 70 mg/mL, or (C) both (A) and (B),

optionally, further comprising an amino acid aggregation inhibitor comprising an aromatic amino acid, such as phenylalanine and tryptophan.

2. The aqueous pharmaceutical formulation of claim 1, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises a light chain variable domain comprising a light chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 5.

3. The aqueous pharmaceutical formulation of claim 2, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises a light chain variable domain comprising a light chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 6, optionally, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises a heavy chain variable domain comprising a heavy chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO: 10.

4. The aqueous pharmaceutical formulation of 2 or 3, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises (i) a light chain variable domain comprising a light chain CDR3 sequence comprising the amino acid sequence set forth in SEQ ID NO:7; (ii) a heavy chain variable domain comprising a heavy chain CDR1 sequence comprising the amino acid sequence set forth in SEQ ID NO: 8; (iii) a heavy chain variable domain comprising a heavy chain CDR2 sequence comprising the amino acid sequence set forth in SEQ ID NO: 9, or (iv) any combination thereof, optionally, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises (A) a light chain variable domain comprising a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 5, a light chain variable domain comprising a light chain CDR2 comprising the amino acid sequence of

SEQ ID NO: 6, and a light chain variable domain comprising a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:7; and (B) a heavy chain variable domain comprising a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 8, a heavy chain variable domain comprising a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 9, and a heavy chain variable domain comprising a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 10.

5. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises:

(A) a light chain variable domain selected from the group consisting of:

- i. a light chain variable domain comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 1;
- ii. a light chain variable domain comprising an amino acid sequence encoded by a polynucleotide sequence comprising SEQ ID NO: 19;
- iii. a light chain variable domain comprising an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO: 19; or

(B) a heavy chain variable domain selected from the group consisting of:

- i. a heavy chain variable domain comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 2;
- ii. a heavy chain variable domain comprising an amino acid sequence encoded by a polynucleotide sequence comprising SEQ ID NO: 20.
- iii. a heavy chain variable domain comprising an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO: 20; or

(C) a light chain variable domain of (A) and a heavy chain variable domain of (B).

6. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the anti-RANKL antibody is (A) a fully human antibody, a humanized antibody, or a

chimeric antibody or (B) an a Fab, Fab', F(ab')₂, or a single chain Fv, or (C) an IgG₁, IgG₂, or IgG₄ antibody, optionally, comprising kappa light chains, optionally, wherein the anti-RANKL antibody comprises a sequence of SEQ ID NO: 15 or comprises a sequence of SEQ ID NO: 16, SEQ ID NO: 17, or SEQ ID NO: 18.

7. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the anti-RANKL antibody, or antigen-binding portion thereof, comprises:

(A) a light chain selected from the group consisting of:

- i. a light chain comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 3 or SEQ ID NO: 13;
- ii. a light chain comprising an amino acid sequence encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 21 or 23;
- iii. a light chain comprising an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO: 21 or 23; or

(B) a heavy chain selected from the group consisting of:

- i. a heavy chain comprising an amino acid sequence that is at least 80% identical to SEQ ID NO: 4 or SEQ ID NO: 14;
- ii. a heavy chain comprising an amino acid sequence encoded by a polynucleotide sequence that is at least 80% identical to SEQ ID NO: 22 or 24.
- iii. a heavy chain comprising an amino acid sequence encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide consisting of SEQ ID NO: 22 or 24; or

(C) a light chain variable domain of (A) and a heavy chain variable domain of (B).

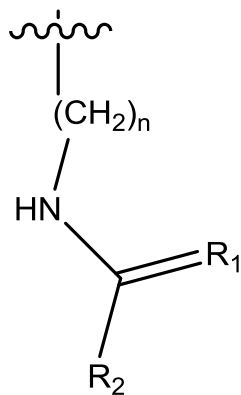
8. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the antibody, or antigen-binding portion thereof, is (A) greater than

70 mg/mL, optionally, in a range of about 70 mg/mL to about 300 mg/mL or (B) in a range of greater than 70 mg/mL to about 300 mg/mL, optionally in a range of greater than about 70 mg/mL to about 200 mg/mL or (C) in a range of about 100 to about 140 mg/mL.

9. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the concentration of the antibody or antigen-binding portion thereof is about 120 mg/mL $\pm$ 12 mg/mL.

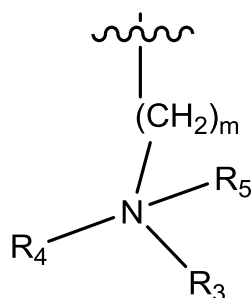
10. The aqueous pharmaceutical formulation of any one of the preceding claims, further comprising an amino acid aggregation inhibitor, optionally, wherein the amino acid aggregation inhibitor comprises an amino acid comprising a charged side chain, an aromatic amino acid, or a hydrophobic amino acid.

11. The aqueous pharmaceutical formulation of claim 10, wherein the amino acid comprising a charged side chain is an amino acid comprising a positive-charged side chain, optionally, wherein the amino acid comprising a positive-charged side chain comprises a side chain structure of Formula I or Formula II:



[Formula I]

wherein n is 1 to 7, wherein each of R_1 and R_2 is independently selected from the group consisting of H, C_1 - C_{18} alkyl, $(C_1$ - C_{18} alkyl)OH, $(C_1$ - C_{18} alkyl) NH_2 , NH , NH_2 (C_1 - C_{18} alkyl)SH, $(C_0$ - C_4 alkyl)(C_3 - C_6)cycloalkyl, $(C_0$ - C_4 alkyl)(C_2 - C_5 heterocyclic), $(C_0$ - C_4 alkyl)(C_6 - C_{10} aryl) R_7 , and $(C_1$ - C_4 alkyl)(C_3 - C_9 heteroaryl), wherein R_7 is H or OH, wherein optionally one of R_1 and R_2 is a free amino group ($-NH_3^+$),



[Formula II]

wherein m is 1 to 7, wherein each of R₃ and R₄ is independently selected from Group A consisting of: H, C₁-C₁₈ alkyl, (C₁-C₁₈ alkyl)OH, (C₁-C₁₈ alkyl)NH₂, (C₁-C₁₈ alkyl)SH, (C₀-C₄ alkyl)(C₃-C₆)cycloalkyl, (C₀-C₄ alkyl)(C₂-C₅ heterocyclic), (C₀-C₄ alkyl)(C₆-C₁₀ aryl)R₈, and (C₁-C₄ alkyl)(C₃-C₉ heteroaryl), wherein R₈ is H or OH, wherein, R₅ is optionally present, and, when present, is selected from Group A, optionally, wherein each of R₃ and R₄ and R₅ is H.

12. The aqueous pharmaceutical formulation of claim 11, wherein n is in a range of 2 to 4, optionally, wherein R₁ is NH or NH₂ or m is in a range of 3 to 5.

13. The aqueous pharmaceutical formulation of claim 12, wherein R₂ is NH₂ or NH₃⁺. optionally, wherein the amino acid comprising a positive-charged side chain is arginine

14. The aqueous pharmaceutical formulation of claim 13, wherein each of R₃ and R₄ and, R₅ is optionally present, wherein, when present, R₅ is H, optionally, wherein the amino acid comprising a positive-charged side chain is lysine.

15. The aqueous pharmaceutical formulation of any one of claims 11 to 14, wherein the amino acid comprising a positive-charged side chain is present in the formulation as a salt, optionally, wherein the salt is a hydrochloride (HCl) salt.

16. The aqueous pharmaceutical formulation of claim 15, comprising L-arginine HCl or L-lysine HCl.

17. The aqueous pharmaceutical formulation of claim 10, wherein the aromatic amino acid comprises a phenyl or an indole, optionally, wherein the aromatic amino acid comprises a C₁-C₆ alkyl chain between the alpha carbon and the phenyl or indole.

18. The aqueous pharmaceutical formulation of claim 17, wherein the alkyl chain is a C₁-C₃ alkyl chain.

19. The aqueous pharmaceutical formulation of claim 18, wherein the aromatic amino acid is L-phenylalanine.

20. The aqueous pharmaceutical formulation of claim 18, wherein the aromatic amino acid is L-tryptophan.

21. The aqueous pharmaceutical formulation of claim 10, wherein the hydrophobic amino acid has a score greater than about 2.5 on the Kyte and Doolittle hydrophobicity scale, optionally, wherein the hydrophobic amino acid comprises a side chain comprising a C₂ to C₁₂ alkyl, branched or straight-chained, or a C₄ to C₈ cycloalkyl, a C₄ to C₈ heterocycle comprising a nitrogen heteroatom, optionally, wherein the heterocycle is an imidazole, pyrrole, or indole.

22. The aqueous pharmaceutical formulation of claim 21, wherein the hydrophobic amino acid comprises a C₃ to C₈ alkyl, optionally, a branched C₃ alkyl or branched C₄ alkyl.

23. The aqueous pharmaceutical formulation of claim 22, wherein the hydrophobic amino acid is L-valine, L-leucine, or L-isoleucine.

24. The aqueous pharmaceutical formulation of any one of the preceding claims, comprising about 5 mM to about 300 mM amino acid aggregation inhibitor, optionally, comprising about 25 mM to about 90 mM amino acid aggregation inhibitor.

25. The aqueous pharmaceutical formulation of claim 24, comprising about 5 mM to about 150 mM amino acid aggregation inhibitor, when the amino acid aggregation inhibitor is an amino acid comprising a positive-charged side chain, optionally, L-arginine, optionally, comprising about 30 mM to about 80 mM amino acid aggregation inhibitor.

26. The aqueous pharmaceutical formulation of claim 24, comprising about 5 mM to about 180 mM amino acid aggregation inhibitor, when the amino acid aggregation inhibitor is an aromatic amino acid, optionally, L-phenylalanine, optionally, comprising about 5 mM to about 100 mM amino acid aggregation inhibitor, optionally, about 20 mM to about 50 mM amino acid

aggregation inhibitor, when the amino acid aggregation inhibitor is an aromatic amino acid, optionally, L-phenylalanine.

27. The aqueous pharmaceutical formulation of claim 24, comprising about 5 mM to about 300 mM amino acid aggregation inhibitor, when the amino acid aggregation inhibitor is a hydrophobic amino acid, optionally, L-valine, L-isoleucine, or L-leucine, optionally, comprising about 5 mM to about 200 mM amino acid aggregation inhibitor, optionally, about 20 mM to about 50 mM amino acid aggregation inhibitor, when the amino acid aggregation inhibitor is a hydrophobic amino acid, optionally, L-valine, L-isoleucine, or L-leucine.

28. The aqueous pharmaceutical formulation of any one of claims 24 to 27, comprising:

- a. about 30 mM to about 80 mM L-arginine hydrochloride;
- b. about 20 mM to about 50 mM L-phenylalanine;
- c. about 20 mM to about 50 mM L-tryptophan;
- d. about 30 mM to about 80 mM L-lysine hydrochloride;
- e. about 20 mM to about 50 mM L-leucine;
- f. about 20 mM to about 50 mM L-isoleucine;
- g. about 20 mM to about 50 mM L-valine; or
- h. any combination thereof.

29. The aqueous pharmaceutical formulation of any one of the preceding claims comprising only one amino acid aggregation inhibitor.

30. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the molar ratio of the amino acid aggregation inhibitor to the anti-RANKL antibody is about 10 to 200, when the amino acid aggregation inhibitor is an aromatic amino acid, optionally, L-phenylalanine, optionally, wherein the molar ratio is about 20 to about 90.

31. The aqueous pharmaceutical formulation of any one of the preceding claims, wherein the molar ratio of the amino acid aggregation inhibitor to the anti-RANKL antibody is about 20 to 300, when the amino acid aggregation inhibitor is an amino acid comprising a

positive-charged side chain, optionally, L-arginine, optionally, wherein the molar ratio is about 45 to 180.

32. The aqueous pharmaceutical formulation of any one of the preceding claims, further comprising (A) a tonicity modifier, optionally, selected from the group consisting of: sorbitol, mannitol, sucrose, trehalose, glycerol, and combinations thereof, (B) a surfactant, (C) a buffer, optionally, wherein the buffer is centered, at 25 °C, in a range of about pH 4.0 to about pH 5.5, or (D) any combination thereof.

33. The aqueous pharmaceutical formulation of claim 32, wherein (A) the tonicity modifier comprises sorbitol or (B) the formulation comprises about 1.0 (w/w)% to about 5.0 (w/w)% tonicity modifier, optionally, comprising about 2.0 (w/w) % to about 5.0 (w/w) % sorbitol, or about 3.5 (w/w) % to about 5.0 (w/w) % sorbitol, or about 4.0% (w/w) to about 5.0 (w/w) % sorbitol, or (C) both (A) and (B).

34. The aqueous pharmaceutical formulation of any one of preceding claims, which is free of sorbitol and, optionally, free of any tonicity modifier.

35. The aqueous pharmaceutical formulation of claim 34, wherein the surfactant is selected from the group consisting of: polyoxyethylene sorbitan fatty acid esters (e.g. polysorbate 20, polysorbate 80), or one or more alkylaryl polyethers, e.g. oxyethylated alkyl phenol (e.g. Triton® X-100), or one or more poloxamers (e.g. Pluronic®, e.g. Pluronic® F68), and combinations thereof.

36. The aqueous pharmaceutical formulation of claim 35, wherein the surfactant is polysorbate 20.

37. The aqueous pharmaceutical formulation of claim 34 or 35 comprising at least about 0.004 (w/v) % surfactant and, optionally, comprising less than 0.15 (w/v)% surfactant, optionally, about 0.005 (w/v) % to about 0.015 (w/v) % surfactant.

38. The aqueous pharmaceutical formulation of claim 32, wherein the buffer has a pKa within one pH unit of pH 5.0-5.2 at 25 °C.

39. The aqueous pharmaceutical formulation of claim 32 or 38, comprising about 5 mM to about 60 mM buffer, optionally, about 5 mM to about 50 mM buffer or about 9 mM to about 45 mM buffer.

40. The aqueous pharmaceutical formulation of any one of claims 32 to 39, wherein the buffer is acetate or glutamate.

41. The aqueous pharmaceutical formulation of any one of the preceding claims, having a pH in a range of about 5.0 to 5.19, optionally, having a pH in a range of about 5.0 to about 5.15, optionally, about 5.0 to about 5.1.

42. The aqueous pharmaceutical formulation of any one of the preceding claims, having a pH in a range of about 5.0 to about 5.4, or about 5.0 to about 5.2, or about 5.0 to less than 5.2, or about 5.0 to 5.19, or about 5.0 to about 5.15, or about 5.0 to about 5.1, optionally, having a pH of about 5.1.

43. The aqueous pharmaceutical formulation of any one of the preceding claims, (I) having a viscosity that is (A) not more than about 6 cP at 5 °C, optionally, wherein the viscosity is about 4.5 cP to about 5.5 cP or (B) less than about 13 cP at 25 °C or (C) in a range of about 2.0 cP to about 10 cP, optionally, about 2.5 cP to about 4 cP, (II) having a conductivity in a range of about 500 μ S/cm to about 5500 μ S/cm, optionally, wherein the conductivity is in a range of about 2500 μ S/cm to about 5500 μ S/cm, when the formulation comprises an amino acid comprising a positive-charged side chain, or in a range of about 500 μ S/cm to about 2000 μ S/cm, when the formulation comprises an aromatic amino acid or lacks an amino acid aggregation inhibitor or (III) having an osmolality in a range of about 200 mOsm/kg to about 500 mOsm/kg, or about 225 mOsm/kg to about 400 mOsm/kg, or about 250 mOsm/kg to about 350 mOsm/kg.

44. The aqueous pharmaceutical formulation of any one of the preceding claims, comprising less than 2% high molecular weight species (HMWS) and/or more than 98% of the antibody main peak, as measured by SE-UHPLC, following (A) storage at about 2 °C to about 8 °C for at least 12 months, 24 months, or 36 months or (B) storage at about 20 °C to about 30 °C for about 1 month or (C) a first storage at about 2 °C to about 8 °C for at least 12 months, 24

months, or 36 months and a second storage at about 20 °C to about 30 °C for about 1 month or (D) storage for about one month at 37 °C or for 3 months at 30 °C.

45. A container, optionally, a vial, pre-filled syringe (PFS), or glass container containing an aqueous pharmaceutical formulation of any one of the preceding claims, optionally, containing about 1 mL or less of the formulation, optionally, about 0.5 mL.

46. A formulation comprising denosumab at a concentration of about 108 mg/mL to about 132 mg/mL, about 28.8 mM to about 35.2 mM acetate, 33.3 mM to about 40.7 mM phenylalanine, 3.51% (w/v) to about 4.29% (w/v) sorbitol, and about 0.009% (w/v) to about 0.011% (w/v) polysorbate 20, at pH 5.1.

47. An aqueous pharmaceutical formulation of any one of claims 1-44, container of claim 45 or formulation of claim 46 for use in therapy.

48. Use of an aqueous pharmaceutical formulation of any one of claims 1-44, container of claim 45 or formulation of claim 46 in the manufacture of a medicament for (a) treatment or prevention of an SRE in a subject with bone metastases from solid tumors, (b) treatment or prevention of an SRE in a subject who is an adult or a skeletally mature adolescent with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, (c) treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy in a subject, (d) treatment or prevention of an SRE in a subject with multiple myeloma or with bone metastases from a solid tumor, (e) treatment of osteoporosis of postmenopausal women at high risk for fracture, (f) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, (g) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, (h) treatment to increase bone mass in men with osteoporosis at high risk for fracture, (i) therapy with calcium or vitamin D, (j) treating giant cell tumor of bone in a patient in need thereof, (k) treating hypercalcemia of malignancy in a patient in need thereof, (l) treating osteoporosis in a patient in need thereof, (m) increasing bone mass in a patient in need thereof.