METHODS OF TREATING OSTEOGENESIS IMPERFECTA

INCORPORATION BY REFERENCE OF THE SEQUENCE LISTING

[0001] This application contains, as a separate part of disclosure, a Sequence Listing in computer-readable form (Filename: 70050_SeqListing.xml; Size: 528,265 bytes; Created: March 27, 2025) which is incorporated by reference herein in its entirety.

FIELD

[0002] The disclosure generally relates to methods of using anti-sclerostin antibodies to treat pediatric osteogenesis imperfecta.

BACKGROUND

[0003] Osteogenesis imperfecta (OI) is a group of genetic skeletal disorders characterized by increased bone fragility, low bone mass (Rauch and Glorieux, Lancet, 363:1377-1385, 2004), and increased bone turnover contributing to osteoporosis, fractures, and other conditions. The medical management of pediatric OI includes the orthopedic prevention and treatment of fractures, bowing, and scoliosis. There are no approved medicinal products for the treatment of OI in children except for neridronate and pamidronate, approved for the treatment of OI in Italy and Japan, respectively. Clinicians have been using bisphosphonates in children with moderate to severe OI to reduce osteoclast activity and increase bone mineral density (BMD) (even though abnormal collagen is usually present [Byers, Curr. Opin. Pediatr. 12:603-609, 2000]) with the aim of reducing fractures (Ward et al, Calcif. Tissue Int., 98:566-572, 2016; Rauch and Glorieux, supra). Teriparatide, an osteoanabolic agent, has been shown to increase bone mass and strength in adults with OI, though its benefit in children is not known (Orwoll et al, J. Clin. Invest., 124:491-498, 2014). Thus, an unmet need remains in children with OI.

SUMMARY

[0004] The disclosure provides a method for treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

BRIEF DESCRIPTION OF THE FIGURES

[0005] Figure 1 is a graph showing that across both the age groups, romosozumab exhibited nonlinear PK at lower doses of 1 and 3 mg/kg. The PK approached linearity at 5 mg/kg.

[0006] Figures 2A and 2B are graphs showing the P1NP percent change from baseline in adolescents (Figure 2A) and children (Figure 2B).

[0007] Figures 3A and 3B are graphs showing the CTX percent change from baseline in adolescents (Figure 3A) and children (Figure 3B).

[0008] Figures 4A and 4B are graphs showing the mean (±SD) lumbar spine bone mineral density (BMD) percent change from baseline in adolescents (Figure 4A) and children (Figure 4B).

[0009] Figures 5A and 5B are graphs showing the mean (±SD) lumbar spine bone mineral density (BMD) Z-score change from baseline in adolescents (Figure 5A) and children (Figure 5B).

DETAILED DESCRIPTION

[0010] The present disclosure is based on the discovery that administering an anti-sclerostin antibody (e.g., romosozumab) to pediatric subjects suffering from osteogenesis imperfecta had a therapeutic effect. As demonstrated in the Example, a trend of dose-related increases was observed in P1NP, lumbar spine BMD, and BMD Z-score values in both adolescents and children.

[0011] In one aspect, described herein is a method of treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

[0012] In some embodiments, the anti-sclerostin antibody is administered for a treatment period, about 1 month to about 12 months (e.g., about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, or about 11 months). In some embodiments, the anti-sclerostin antibody is administered once a month for 12 months.

[0013] In some embodiments, the methods described herein further comprises administering vitamin D to the subject,

[0014] The dose of anti-sclerostin antibody administered may range from about 0.5 mg/kg to about 20 mg/kg (e.g., 12 mg/kg) of body weight. For example, the dose of anti-sclerostin antibody may range from about 1 mg/kg to about 10 mg/kg (e.g., about 2 mg/kg, about 3

mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, or about 9 mg/kg), about 1 mg/kg to about 3 mg/kg, about 3 mg/kg to about 8 mg/kg (e.g., about 4 mg/kg, 5 mg/kg, 6 mg/kg, or 7 mg/kg) or about 1 mg/kg to about 5 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 1 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 3 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 5 mg/kg.

[0015] In various embodiments, the method comprises administering from about 50 milligrams to about 1,000 milligrams of the anti-sclerostin antibody to the subject (e.g., a human subject). For example, a dose of anti-sclerostin antibody can comprise at least about 5 mg, 15 mg, 25 mg, 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 150 mg, about 200 mg, about 210, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg or up to about 1,000 mg of anti-sclerostin antibody. Ranges between any and all of these endpoints are also contemplated, e.g. about 50 mg to about 80 mg, about 70 mg to about 140 mg, about 70 mg to about 270 mg, about 75 mg to about 100 mg, about 100 mg to about 150 mg, about 140 mg to about 210 mg, or about 150 mg to about 200 mg, or about 180 mg to about 270 mg, or about 280 to about 410 mg. The dose is administered at any interval, such as multiple times a week (e.g., twice or three times per week), once a week, once every two weeks, once every three weeks, or once every four weeks. In some or any embodiments, a dose of anti-sclerostin antibody ranging from about 120 mg to about 210 mg is administered once a month. In some or any embodiments, a dose of about 210 mg of the anti-sclerostin antibody is administered once month for 12 months.

[0016] In addition, it may be advantageous to administer multiple doses of an anti-sclerostin antibody or space out the administration of doses, depending on the therapeutic regimen selected for a particular patient. The anti-sclerostin antibody can be administered periodically over a time period of one year or less (e.g., 9 months or less, 6 months or less, or 3 months or less). In this regard, the anti-sclerostin antibody can be administered to the subject once every about 7 days, or 2 weeks, or 3 weeks, or 1 month, or 5 weeks, or 6 weeks, or 7 weeks, or 2 months, or 9 weeks, or 10 weeks, or 11 weeks, or 3 months, or 13 weeks, or 14 weeks, or 15 weeks, or 4 months, or 17 weeks, or 18 weeks, or 19 weeks, or 5 months, or 21 weeks, or 22 weeks, or 23 weeks, or 6 months, or 12 months.

[0017] An “anti-sclerostin antibody” specifically binds to sclerostin or portions thereof to block or impair binding of human sclerostin to one or more ligands. Sclerostin, the product of the SOST gene, is absent in sclerosteosis, a skeletal disease characterized by bone overgrowth and strong dense bones (Brunkow et al., *Am. J. Hum. Genet.*, *68*:577-589

(2001); Balemans et al., *Hum. Mol. Genet.*, *10*:537-543 (2001)). The amino acid sequence of human sclerostin is reported by Brunkow et al. and is disclosed in U.S. Patent Publication No. 20070110747 as SEQ ID NO: 1 (which patent publication is incorporated in its entirety for its description of anti-sclerostin antibodies and Sequence Listing). Recombinant human sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1406-ST-025). Additionally, recombinant mouse sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1589-ST-025). Research grade sclerostin-binding monoclonal antibodies are commercially available from R&D Systems (Minneapolis, Minn., USA; mouse monoclonal: 2006 Catalog # MAB1406; rat monoclonal: 2006 Catalog # MAB1589). U.S. Patent Nos. 6,395,511 and 6,803,453, and U.S. Patent Publication Nos. 20040009535 and 20050106683 refer to anti-sclerostin antibodies generally. Examples of anti-sclerostin antibodies suitable for use in the context of the invention also are described in U.S. Patent Publication Nos. 20070110747 and 20070072797, which are hereby incorporated by reference. Additional information regarding materials and methods for generating anti-sclerostin antibodies can be found in U.S. Patent Publication No. 20040158045.

[0018] The term "antibody" refers to an intact antibody. An antibody may comprise a complete antibody molecule (including, but not limited to, polyclonal, monoclonal, chimeric, humanized, or human versions having full length heavy and/or light chains). Antibody polypeptides, including fibronectin polypeptide monobodies, also are disclosed in U.S. Patent No. 6,703,199. Other antibody polypeptides are disclosed in U.S. Patent Publication No. 20050238646. Anti-sclerostin antibodies may bind to sclerostin of SEQ ID NO: 1, or a naturally occurring variant thereof, with an affinity of less than or equal to 1×10^{-7}M, less than or equal to 1×10^{-8}M, less than or equal to 1×10^{-9}M, less than or equal to 1×10^{-10}M, less than or equal to 1×10^{-11}M, or less than or equal to 1×10^{-12} M. Affinity may be determined by an affinity ELISA assay. In certain embodiments, affinity may be determined by a BIAcore assay. In certain embodiments, affinity may be determined by a kinetic method. In certain embodiments, affinity may be determined by an equilibrium/solution method.

[0019] Antibody fragments include $F(ab')_2$, Fab, Fab', Fv, Fc, and Fd fragments, and can be incorporated into single domain antibodies, single-chain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, *Nature Biotechnology*, *23*(9):1126-1136 (2005)). An antibody fragment may be any synthetic or genetically engineered protein. For example, antibody fragments include isolated fragments consisting of the light chain variable region, "Fv" fragments consisting of the variable regions of the heavy and light chains, recombinant

single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker (scFv proteins).

[0020] Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs (also termed "minimal recognition units" or "hypervariable region") can be obtained by constructing polynucleotides that encode the CDR of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology, 2*:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies Production, Engineering and Clinical Application*, Ritter et al. (eds.), page 166, Cambridge University Press (1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al., (eds.), page 137, Wiley-Liss, Inc. (1995)).

[0021] In some embodiments, the anti-sclerostin antibody cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747) to sclerostin. Alternatively or in addition, the anti-sclerostin antibody is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747). The terms "cross-block," "cross-blocked," and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to sclerostin. The extent to which an antibody or other binding agent is able to interfere with the binding of another to sclerostin, and therefore whether it can be said to cross-block, can be determined using competition binding assays. In some aspects, a cross-blocking antibody or fragment thereof reduces sclerostin binding of a reference antibody between about 40% and about 100%, such as about 60% and about 100%, specifically between 70% and 100%, and more specifically between 80% and 100%. A particularly suitable quantitative assay for detecting cross-blocking uses a Biacore machine which measures the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between antibodies or other binding agents in terms of their binding to sclerostin.

[0022] Suitable anti-sclerostin antibodies include antibodies described in U.S. Patent Publication No. 20070110747, such as one or more of CDR-H1, CDR-H2, CDR-H3, CDR-

L1, CDR-L2 and CDR-L3 as specifically disclosed therein. At least one of the regions of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 may have at least one amino acid substitution, provided that the binding agent retains the binding specificity of the non-substituted CDR. The non-CDR portion of the binding agent may be a non-protein molecule, wherein the binding agent cross-blocks the binding of an antibody disclosed herein to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be a non-protein molecule in which the binding agent exhibits a similar binding pattern to human sclerostin peptides in a human sclerostin peptide epitope competition binding assay as that exhibited by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein or a synthetic peptide, and the recombinant binding protein cross-blocks the binding of an antibody to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein, and the recombinant binding protein exhibits a similar binding pattern to human sclerostin peptides in the human sclerostin peptide epitope competition binding assay (described in U.S. Patent Publication No. 20070110747) as that exhibited by at least one of the antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. Preferably, the anti-sclerostin antibody is Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, or Ab-24 of U.S. Patent Publication No. 20070110747.

[0023] In addition, the anti-sclerostin antibody can comprise at least one CDR sequence having at least 75% identity (e.g., at least 80%, 90%, or 100% identity) to a CDR selected from SEQ ID NOs: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 78, 79, 80, 81, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 351, 352, 353, 358, 359, and 360 disclosed in U.S. Patent Publication No. 20070110747. Preferably, the anti-sclerostin antibody comprises at least one CDR sequence having at least 75% identity (e.g., at least 80%, 90%, or 100% identity) to a CDR selected from SEQ ID NOs: 245, 246, 247,

78, 79, 80, 269, 270, 271, 239, 240, and 24. In some embodiments, the anti-sclerostin antibody comprises: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

[0024] In some embodiments, the anti-sclerostin antibody comprises at least one CDR sequence having at least 75% (e.g., at least 80%, 90%, or 100% identity) identity to a CDR selected from CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 wherein CDR-H1 has the sequence given in SEQ ID NO: 245 or SEQ ID NO: 269, CDR-H2 has the sequence given in SEQ ID NO: 246 or SEQ ID NO: 270, CDR-H3 has the sequence given in SEQ ID NO: 247 or SEQ ID NO: 271, CDR-L1 has the sequence given in SEQ ID NO: 78 or SEQ ID NO: 239, CDR-L2 has the sequence given in SEQ ID NO: 79 or SEQ ID NO: 240 and CDR-L3 has the sequence given in SEQ ID NO: 80 or SEQ ID NO 241.In some embodiments, the anti-sclerostin antibody comprises a set of 6 CDRS.

[0025] Alternatively, the anti-sclerostin antibody can have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 137 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least

80%, 90%, or 100% identity) to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2 and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 133 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80.

[0026] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 141 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80, respectively.

[0027] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 335 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 334 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241, respectively.

[0028] Alternatively, the anti-sclerostin antibody has a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 331 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 330 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241, respectively.

[0029] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 341 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241.

[0030] Alternatively, the anti-sclerostin antibody has a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 137, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 133; or a heavy chain

comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 141; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 335, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 334; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 331, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 330; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 341.

[0031] In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 145 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 141.

[0032] Examples of other anti-sclerostin antibodies include, but are not limited to, the anti-sclerostin antibodies disclosed in International Patent Publication Nos. WO 2008/092894, WO 2008/115732, WO 2009/056634, WO 2009/047356, WO 2010/100200, WO 2010/100179, WO 2010/115932, and WO 2010/130830 (each of which is incorporated by reference herein in its entirety).

[0033] It will be understood by one skilled in the art that some proteins, such as antibodies, may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the protein as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperizine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, RJ. *Journal of Chromatography* 705:129-134, 1995).

[0034] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, pp. 79-86 [1983], entirely incorporated by reference), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0035] In some or any embodiments, the C-terminus of the heavy chain of the antibody, comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397), is amidated. In some or any embodiments, both heavy chains of the antibody comprise the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) and both heavy chains are amidated. In some embodiments, the glycine is amidated. Amidation can occur, e.g., as described in Prigg, S.

T. et al., “New insights into copper monooxygenases and peptide amidation: structure, mechanism and function”, Cell. Mol. Life Sci. 57 (2000) 1236–1259. The enzyme peptidylglycine α-amidating monooxygenase (PAM) can catalyze the amidation of glycine. PAM has two active domains, peptidylglycine α-hydroxylating monooxygenase (PHM) and peptidyl-α-hydroxylglycine α-amidating lyase (PAL). PHM catalyzes the conversion of peptidylglycine (along with ascorbate and oxygen) to peptidyl α-hydroxylglycine (along with semidehydrogenascorbate and water). In turn, PAL catalyzes the conversion of peptidyl α-hydroxylglycine to an amidated peptide (and glyoxylate).

[0036] Amidation of an antibody can be controlled by altering certain conditions during the cell culture process. For example, copper (e.g., in ferric ammonium citrate) and/or oxygen levels may be used to influence amidation levels. It is contemplated that increasing copper concentration (e.g., in the media) or oxygen availability (e.g., during culturing) may increase amidation by impacting the activity of an enzyme such as PHM.

[0037] Pharmaceutical Compositions

[0038] In some embodiments, the anti-sclerostin antibody is formulated in a composition together with a pharmaceutically effective diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. Pharmaceutical compositions of the invention include, but are not limited to, liquid, frozen, and lyophilized compositions.

[0039] In some embodiments, the pharmaceutical composition comprises a population of an anti-sclerostin antibody described herein. For example, in some embodiments, the pharmaceutical composition comprises a mixture of antibodies that specifically bind to sclerostin of SEQ ID NO: 1 and a pharmaceutically acceptable carrier, wherein about 3-5% of the antibodies in the composition are a population of antibodies described herein (e.g., antibodies comprising set of six CDRs set forth in SEQ ID NOs: 78-80 and SEQ ID NOs: 245-247 and having a heavy chain (or two heavy chains) comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) at the C-terminus of the heavy chain(s)). The disclosure also contemplates compositions comprising alternative amounts (e.g., 5-10%, 1-3%, 3-15%, 2-10%, 4-20%, 1-5%) of the population of antibodies described herein (e.g., antibodies comprising set of six CDRs set forth in SEQ ID NOs: 78-80 and SEQ ID NOs: 245-247 and having a heavy chain (or two heavy chains) comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) at the C-terminus of the heavy chain(s)).

[0040] In some embodiments, less than 70% of the antibodies of the population (e.g., about 69%, about 68%, about 67%, about 66%, about 65%, about 64%, about 63%, about 62%, about 61%, about 60%, about 59%, about 58%, about 57%, about 56%, about 55%, about 54%, about 53%, about 52%, about 51%, about 50%, about 49%, about 48%, about 47%, about 46%, about 45%, about 44%, about 43%, about 42%, about 41%, about 40%,

about 39%, about 38%, about 37%, about 36%, about 35%, about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) comprise a heavy chain comprising a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence, which is optionally amidated. In some embodiments, less than 35% (e.g., about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) of the antibodies of the population comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence on both heavy chains, where both heavy chains are optionally amidated. It is also contemplated that both heavy chains comprise the C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence but only one of the chains is amidated. In some embodiments, less than 35% (e.g., about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) of the antibodies in the composition comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence that is not amidated. In some embodiments, about 33% of antibodies of the population comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence that is amidated, about 33% of the antibodies of the population comprise C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequences on both heavy chains which are both amidated, and about 33% of the antibodies of the population comprise heavy chain(s) with a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence but which are not amidated.

[0041] In some embodiments, the pharmaceutical composition contains formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, proline, or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers;

monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18" Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

[0042] Selection of the particular formulation materials described herein may be driven by, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, supra. The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor. In certain embodiments, the composition may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in some embodiments, the antibody or fragment may be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0043] The pharmaceutical compositions of the invention can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art. The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0044] When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antibody or fragment in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antibody or fragment is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antibody or fragment.

[0045] In some or any embodiments, the pharmaceutical composition described herein comprises a calcium salt, an acetate buffer, a polyol and a surfactant. Exemplary calcium salts include, but are not limited to, calcium acetate, calcium carbonate and calcium chloride. In some embodiments, the calcium salt is at a concentration of at least 0.5 mM, at least 1 mM, at least 2 mM, at least 3 mM, at least 4 mM, at least 5 mM, at least 6 mM, at least 7 mM, at least 8 mM, at least 9 mM or at least 10 mM. In certain embodiments, the concentration of calcium salt is not greater than 11 mM, no greater than 12 mM, no greater than 13 mM, no greater than 14 mM, no greater than 15 mM, no greater than 16 mM, no greater than 17 mM, no greater than 18 mM, no greater than 19 mM, no greater than 20 mM, no greater than 21 mM, no greater than 22 mM, no greater than 23 mM, no greater than 24 mM, or no greater than 25 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 0.5 mM to about 10 mM, about 5 mM to about 10 mM, or about 5 mM to about 15 mM.

[0046] In some embodiments, the pharmaceutical composition comprises an acetate buffer (e.g., sodium acetate) having a concentration ranging from about 0.1 mM to about 1000 mM (1 M). In some embodiments, the concentration of the acetate buffer is at least 5 mM, at least 6 mM, at least 7 mM, at least 8 mM, at least 9 mM, at least 10 mM, at least 15 mM, at least 60 mM, at least 70 mM, at least 80 mM, at least 90 mM, at least 100 mM, at least 200 mM, at least 500 mM, at least 700 mM, or at least 900 mM. In some embodiments, the concentration of the acetate buffer is no greater than 10 mM, no greater than 15 mM, no greater than 20 mM, no greater than 25 mM, no greater than 30 mM, no greater than 35 mM, no greater than 40 mM, no greater than 45 mM, no greater than 50 mM, no greater than 55 mM, no greater than 60 mM, no greater than 65 mM, no greater than 70 mM, no greater than 75 mM, no greater than 80 mM, no greater than 85 mM, no greater than 90 mM, no greater than 95 mM or no greater than 100 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 5 mM to about 15 mM, or from about 5 mM to about 10 mM or from about 10 mM to about 25 mM. The buffer is preferably added to a concentration that maintains pH around 5-6 or 5-5.5 or 4.5-5.5. When the calcium salt in the formulation is calcium acetate, in some

embodiments, the total concentration of acetate is about 10 mM to about 55 mM, or about 20 mM to about 40 mM.

[0047] In some aspects, the pharmaceutical composition comprises a total concentration of acetate that is at least about 10 mM, at least about 15 mM, at least about 20 mM, at least about 25 mM, at least about 30 mM, at least about 35 mM, at least about 40 mM, 45 mM, or 50 mM. In some embodiments, the concentration of acetate is no greater than about 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. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 10 mM to about 50 mM, about 20 mM to about 50 mM, about 20 mM to about 40 mM, about 30 mM to about 50 mM, or about 30 mM to about 75 mM. In some embodiments, the calcium salt is calcium acetate and the acetate buffer is sodium acetate. By way of nonlimiting example, a solution containing 10 mM calcium acetate will have 20 mM acetate anion and 10 mM of calcium cation, because of the divalent nature of the calcium cation, while a solution containing 10 mM sodium acetate will have 10 mM sodium cation and 10 mM acetate anion.

[0048] In some embodiments, the total concentration of ions (cations and anions) in solution is at least 10 mM, at least about 15 mM, at least about 20 mM, at least about 25 mM, at least about 30 mM, at least about 35 mM, at least about 40 mM, at least about 45 mM, at least about 50 mM, at least about 55 mM, at least about 60 mM, at least about 65 mM, at least about 70 mM, at least about 75 mM, at least about 80 mM, or at least about 85 mM. In some embodiments, the total concentration of ions is no greater than about 30 mM, no greater than about 35 mM, no greater than about 40 mM, no greater than about 45 mM, no greater than about 50 mM, no greater than about 55 mM, no greater than about 60 mM, no greater than about 65 mM, no greater than about 70 mM, no greater than about 75 mM, no greater than about 80 mM, no greater than about 85 mM, no greater than about 90 mM, no greater than about 95 mM, no greater than about 100 mM, no greater than about 110 mM, no greater than about 120 mM, no greater than about 130 mM, no greater than about 140 mM, no greater than about 150 mM, no greater than about 160 mM, no greater than about 170 mM, no greater than about 180 mM, no greater than about 190 mM or no greater than about 200 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 30 mM to about 60 mM, or about 30 mM to about 70 mM, or about 30 mM to about 80 mM, or about 40 mM to about 150 mM, or about 50 mM to about 150 mM. By way of nonlimiting example, a solution of 10 mM calcium acetate will have a 30 mM total concentration of ions (10 mM cations and 20 mM anions).

[0049] In some or any embodiments, the pharmaceutical composition comprises a polyol. Polyols encompass a class of excipients that includes sugars (e.g. mannitol, sucrose, sorbitol) and other polyhydric alcohols (e.g., glycerol and propylene glycol). Exemplary

polyols include, but are not limited to, propylene glycol, glycerin (glycerol), threose, threitol, erythrose, erythritol, ribose, arabinose, arabitol, lyxose, maltitol, sorbitol, sorbose, glucose, mannose, mannitol, levulose, dextrose, maltose, trehalose, fructose, xylitol, inositol, galactose, xylose, fructose, sucrose, 1,2,6-hexanetriol and the like. Higher order sugars include, but are not limited to, dextran, propylene glycol, or polyethylene glycol. Reducing sugars such as fructose, maltose or galactose oxidize more readily than do non-reducing sugars. Additional examples of sugar alcohols are glucitol, maltitol, lactitol or iso-maltulose. Additional exemplary lyoprotectants include glycerin and gelatin, and the sugars mellibiose, melezitose, raffinose, mannotriose, and stachyose. Examples of reducing sugars include glucose, maltose, lactose, maltulose, iso-maltulose and lactulose. Examples of non-reducing sugars include non-reducing glycosides of polyhydroxy compounds selected from sugar alcohols and other straight chain polyalcohols. Monoglycosides include compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose.

[0050] In some or any embodiments, the pharmaceutical composition comprises a polyol at a concentration ranging from about 0% to about 40% w/v. In some or any embodiments, the compositions comprise a polyol at concentration of at least 0.5, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 30, or at least 40% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 1, 2, 3, 4, 5, 6, 7, 8, 9% to about 10% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 2% to about 6% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 4% w/v. In some or any embodiments, the composition comprises a polyol at about 6% w/v.

[0051] In some or any embodiments, the pharmaceutical composition comprises a surfactant. Exemplary surfactants include, but are not limited to, anionic, cationic, nonionic, zwitterionic, and amphoteric surfactants including surfactants derived from naturally-occurring amino acids. Anionic surfactants include, but are not limited to, sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt. Cationic surfactants include, but are not limited to, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Zwitterionic surfactants include, but are not limited to, CHAPS, CHAPSO, SB3-10, and SB3-12. Non-ionic surfactants include, but are not limited to, digitonin, Triton X-100, Triton X-114, TWEEN-20, and TWEEN-80. In another embodiment, surfactants include, but are not limited to, lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil

10, 40, 50 and 60, glycerol monostearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65 and polysorbate 80, soy lecithin and other phospholipids such as DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. In some or any embodiments, the surfactant is polysorbate 20.

[0052] Surfactants may be included in the compositions either individually or as a mixture in different ratios. In some or any embodiments, the composition comprises a surfactant at a concentration of about 0% to about 5% w/v (e.g., about 0.001, about 0.002, about 0.005, about 0.007, about 0.01, about 0.05, about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.5, about 2.0, about 2.5, about 3.0, about 3.5, about 4.0, or about 4.5% w/v). In some or any embodiments, the composition comprises a surfactant at a concentration of about 0.001% to about 0.5% w/v. In some or any embodiments, the composition comprises a surfactant at a a concentration of about 0.004, about 0.005, about 0.007, about 0.01, about 0.05, or about 0.1% w/v to about 0.2% w/v. In some or any embodiments, the composition comprises a surfactant at a concentration of about 0.01% to about 0.1% w/v.

[0053] In some or any embodiments, the pharmaceutical composition comprises 55 mM acetate, 13 mm calcium, 6.0 % (w/v) sucrose, 0.006% (w/v) polysorbate 20, pH 5.2.

[0054] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antigen binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3773919 and European Patent Application Publication No. EP058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., 1981, supra) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP133988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692; European Patent Application Publication Nos. EP036676; EP088046 and EP143949, incorporated by reference.

[0055] Pharmaceutical compositions used for *in vivo* administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0056] The invention is further described in the following example. The example serves only to illustrate the invention and are not intended to limit the scope of the invention in any way.

EXAMPLE

[0057] The following Example describes a multicenter, open-label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to < 12 years of age) and adolescents (12 to < 18 years of age) with OI.

[0058] Romosozumab is a humanized monoclonal antibody immunoglobulin 2 that binds and inhibits sclerostin and has a dual effect on bone of increasing bone formation and decreasing bone resorption. Romosozumab comprises the CDR sequences set forth in SEQ ID NOs: 78-80 and 245-257; light and heavy variable regions set forth in SEQ ID NOs: 376 and 378, respectively; and light and heavy chains set forth in SEQ ID NOs: 141 and 145, respectively.

[0059] Romosozumab is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture in the United States (US EVENITY Prescribing Information), and severe osteoporosis in postmenopausal women at high risk for fracture in European Union (EU EVENITY Summary of Product Characteristics).

[0060] Proof of biological activity for romosozumab was established in a first-in-human, ascending single-dose study in healthy males and postmenopausal females, an ascending multiple dose study in healthy males and postmenopausal females with low bone mass and in a phase 2 dose-ranging study in postmenopausal females with low bone mass. In all studies, treatment with romosozumab was generally well tolerated and resulted in a transient increase of the bone formation markers procollagen type I N-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase, and a decrease in the bone resorption marker serum type I collagen C-telopeptide (sCTX) (McClung et al, 2014; Padhi et al, 2014; Padhi et al, 2011). With gains in bone mass, the risk for patients to experience an osteoporotic fracture can be lessened, as demonstrated during the romosozumab phase 3 programs. In this phase 1b, open-label, ascending multiple dose study, the safety,

tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of romosozumab were evaluated in children and adolescents with OI."

[0061] All subjects received 3 subcutaneous (SC) doses of romosozumab every 4 weeks (QM). Subjects in cohort 1 (12 to <18 years of age) and cohort 2 (5 to < 12 years of age) were administered romosozumab 1 mg/kg SC QM. Subjects in cohort 3 (12 to < 18 years of age) and cohort 4 (5 to < 12 years of age) were administered romosozumab 3 mg/kg SC QM. Subjects in cohort 5 (12 to < 18 years of age) and cohort 6 (5 to < 12 years of age) were administered romosozumab 5 mg/kg SC QM. All subjects received daily supplementation with calcium and vitamin D.

[0062] Key Baseline demographics and Characteristics are provided below in Table 1.

	Cohort 1 1 mg/kg (n=4)	Cohort 2 1 mg/kg (n=4)	Cohort 3 3 mg/kg (n=4)	Cohort 4 3 mg/kg (n=5)	Cohort 5 5 mg/kg (n=4)	Cohort 6 5 mg/kg (n=4)	Overall (n=25)
Male n (5)	3 (75)	4 (100)	3 (75)	1 (20)	2 (50)	3 (75)	16 (64)
Mean age (years)	14.3	6	14.3	8.4	14	6.5	10.5
Mean body weight (kg)	55.9	19.5	66	26.7	43.6	16.9	37.6
Mean BMI	21.2	15.6	24.1	17.4	23.8	15.5	19.5
Mean lumbar spine BMD (g/cm^2)	0.69	0.35	0.60	0.49	0.74	0.35	0.54
Mean lumbar spine BMP Z-score	-2.43	-3.08	-2.95	-1.9	-1.65	-2.6	-2.57
Type of OI n (%)							
I	3 (75)	3 (75)	3 (75)	1 (20)	2 (50)	2 (50)	14 (56)
II	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
III	0 (0)	1 (25)	1 (25)	4 (80)	2 (50)	2 (50)	10 (40)
IV	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Facture history n (%)							
Yes	4 (100)	4 (100)	4 (100)	5 (100)	4 (100)	4 (100)	25 (100)
Nonveretebral	2 (50)	4 (100)	4 (100)	5 (100)	4 (100)	3 (75)	22 (88)

[0063] Results:

[0064] Twelve of 25 subjects (48.0%) had treatment-emergent adverse events during the study. Serious treatment-emergent adverse events were reported for 2 subjects (8.0%); these events included femur fracture and lower limb fracture. None of these events were considered related to the investigational product by the investigator. The overall study results show that romosozumab was well tolerated in the pediatric population with OI.

[0065] As shown in Figure 1, romosozumab exhibited nonlinear PK at lower doses of 1 and 3 mg/kg across both ae groups. The PK approached linearity at 5 mg/kg.

[0066] As shown in Figure 2, Pharmacokinetics (PK) in pediatric OI subjects was non-linear between 1 and 3 mg/kg, as seen in adults; PK approaches linearity at 5mg/kg.

[0067] A trend of dose-related increases was observed in P1NP, lumbar spine BMD, and BMD Z-score values in both adolescents and children.

[0068] There appeared to be a dose response in elevation of the P1NP levels in both adolescents and children. P1NP levels increased when measured after dosing (on days 8 to 15). The mean percentage change in P1NP levels from baseline ranged from 11.03% to 58.58% at day 15 for the adolescents and from 10.52% to 28.35% at day 15 for the children. P1NP levels returned towards the baseline until next dosing. P1NP levels returned close to baseline by day 113 in both adolescents and children. See Figures 2A and 2B.

[0069] CV% of exposure parameters tend to be lower in 5 mg/kg cohorts relative to lower doses cohorts. Minimal accumulation was observed between the first and third doses, the mean accumulation ratios were generally less than 1. See Figures 3A and 3B.

[0070] Figures 4A and 4B show that there was a trend of dose-related changes in lumbar spine BMC with increase in mean percentage change from baseline ranging from 7.68% to 18.16% at day 85 and from 12.64% to 21.29% at day 169 for the adolescents, and from 8.41% to 16.03% at day 85 and from 7.98% to 12.42% at day 169 for the children.

[0071] Figures 5A and 5B show that most subjects, both adolescents and children, also showed increased lumbar spine BMD Z-scores after 3 monthly doses of romosozumab, with increase in mean BMD Z-scores from baseline ranging from 0.20 to 0.50 at day 85 and from 0.23 to 0.48 at day 169 in the adolescents, and from 0.33 to 0.53 at day 85 and from 0.25 to 0.50 at day 169 in the children.

[0072] All of the references cited herein, including patents, patent applications, literature publications, and the like, are hereby incorporated in their entireties by reference.

[0073] While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred compounds and methods may be used and that it is intended that the invention

may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WHAT IS CLAIMED IS:

1. A method for treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

2. The method of claim 1, comprising administering 1 mg/kg anti-sclerostin antibody to the subject.

3. The method of claim 1, comprising administering 3 mg/kg anti-sclerostin antibody to the subject.

4. The method of claim 1, comprising administering 5 mg/kg anti-sclerostin antibody to the subject.

5. The method of any one of claims 1-4, wherein an amount of the antibody is administered to the subject once a month.

6. The method of any one of claims 1-5, comprising administering 210 mg anti-sclerostin antibody to the subject.

7. The method of any one of claims 1-6, where the antibody cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin.

8. The method of any one of claims 1-7, wherein the antibody is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24.

9. The method of any one of claim 1-8, wherein the antibody comprises: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID

NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

10. The method of claim 9, wherein the antibody comprises CDRH-1, CDR-H2, CDR-H3, CDR-L1 CDR-L2 and CDR-L3 wherein (a) CDR-H1 is SEQ ID NO:245, CDR-H2 is SEQ ID NO:246, CDR-H3 is SEQ ID NO:247, CDR-L1 is SEQ ID NO:78, CDR-L2 is SEQ ID NO:79 and CDR-L3 is SEQ ID NO:80; or (b) CDR-H1 is SEQ ID NO:269, CDR-H2 is SEQ ID NO:270, CDR-H3 is SEQ ID NO:271, CDR-L1 is SEQ ID NO:239, CDR-L2 is SEQ ID NO:240 and CDR-L3 is SEQ ID NO:241.

11. The method of any one of claims 1-10, wherein the antibody is a human antibody, a humanized antibody, a monoclonal antibody, or a chimeric antibody.

12. The method of any one of claims 1-11 further comprising administering vitamin D to the subject.

13. Use of an anti-sclerostin antibody in preparation of a medicament for treating osteogenesis imperfecta in a subject in an amount from about 1 mg/kg to about 10 mg/kg, wherein the wherein the subject is less than 17 years of age.

ABSTRACT

The invention is directed to a method of treating pediatric osteogenesis imperfecta comprising administering an anti-sclerostin antibody to the subject in an amount ranging from 1 mg/kg to 10 mg/kg.

METHODS OF TREATING OSTEOGENESIS IMPERFECTA

INCORPORATION BY REFERENCE OF THE SEQUENCE LISTING

[0001] This application contains, as a separate part of disclosure, a Sequence Listing in computer-readable form (Filename: 70050_SeqListing.xml; Size: 528,265 bytes; Created: March 27, 2025) which is incorporated by reference herein in its entirety.

FIELD

[0002] The disclosure generally relates to methods of using anti-sclerostin antibodies to treat pediatric osteogenesis imperfecta.

BACKGROUND

[0003] Osteogenesis imperfecta (OI) is a group of genetic skeletal disorders characterized by increased bone fragility, low bone mass (Rauch and Glorieux, Lancet, 363:1377-1385, 2004), and increased bone turnover contributing to osteoporosis, fractures, and other conditions. The medical management of pediatric OI includes the orthopedic prevention and treatment of fractures, bowing, and scoliosis. There are no approved medicinal products for the treatment of OI in children except for neridronate and pamidronate, approved for the treatment of OI in Italy and Japan, respectively. Clinicians have been using bisphosphonates in children with moderate to severe OI to reduce osteoclast activity and increase bone mineral density (BMD) (even though abnormal collagen is usually present [Byers, Curr. Opin. Pediatr. 12:603-609, 2000]) with the aim of reducing fractures (Ward et al, Calcif. Tissue Int., 98:566-572, 2016; Rauch and Glorieux, supra). Teriparatide, an osteoanabolic agent, has been shown to increase bone mass and strength in adults with OI, though its benefit in children is not known (Orwoll et al, J. Clin. Invest., 124:491-498, 2014). Thus, an unmet need remains in children with OI.

SUMMARY

[0004] The disclosure provides a method for treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

BRIEF DESCRIPTION OF THE FIGURES

[0005] Figure 1 is a graph showing that across both the age groups, romosozumab exhibited nonlinear PK at lower doses of 1 and 3 mg/kg. The PK approached linearity at 5 mg/kg.

[0006] Figures 2A and 2B are graphs showing the P1NP percent change from baseline in adolescents (Figure 2A) and children (Figure 2B).

[0007] Figures 3A and 3B are graphs showing the CTX percent change from baseline in adolescents (Figure 3A) and children (Figure 3B).

[0008] Figures 4A and 4B are graphs showing the mean (±SD) lumbar spine bone mineral density (BMD) percent change from baseline in adolescents (Figure 4A) and children (Figure 4B).

[0009] Figures 5A and 5B are graphs showing the mean (±SD) lumbar spine bone mineral density (BMD) Z-score change from baseline in adolescents (Figure 5A) and children (Figure 5B).

DETAILED DESCRIPTION

[0010] The present disclosure is based on the discovery that administering an anti-sclerostin antibody (e.g., romosozumab) to pediatric subjects suffering from osteogenesis imperfecta had a therapeutic effect. As demonstrated in the Example, a trend of dose-related increases was observed in P1NP, lumbar spine BMD, and BMD Z-score values in both adolescents and children.

[0011] In one aspect, described herein is a method of treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

[0012] In some embodiments, the anti-sclerostin antibody is administered for a treatment period, about 1 month to about 12 months (e.g., about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, or about 11 months). In some embodiments, the anti-sclerostin antibody is administered once a month for 12 months.

[0013] In some embodiments, the methods described herein further comprises administering vitamin D to the subject,

[0014] The dose of anti-sclerostin antibody administered may range from about 0.5 mg/kg to about 20 mg/kg (e.g., 12 mg/kg) of body weight. For example, the dose of anti-sclerostin antibody may range from about 1 mg/kg to about 10 mg/kg (e.g., about 2 mg/kg, about 3

mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, or about 9 mg/kg), about 1 mg/kg to about 3 mg/kg, about 3 mg/kg to about 8 mg/kg (e.g., about 4 mg/kg, 5 mg/kg, 6 mg/kg, or 7 mg/kg) or about 1 mg/kg to about 5 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 1 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 3 mg/kg. In some embodiments, the dose of anti-sclerostin antibody is about 5 mg/kg.

[0015] In various embodiments, the method comprises administering from about 50 milligrams to about 1,000 milligrams of the anti-sclerostin antibody to the subject (e.g., a human subject). For example, a dose of anti-sclerostin antibody can comprise at least about 5 mg, 15 mg, 25 mg, 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 150 mg, about 200 mg, about 210, about 240 mg, about 250 mg, about 280 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg or up to about 1,000 mg of anti-sclerostin antibody. Ranges between any and all of these endpoints are also contemplated, e.g. about 50 mg to about 80 mg, about 70 mg to about 140 mg, about 70 mg to about 270 mg, about 75 mg to about 100 mg, about 100 mg to about 150 mg, about 140 mg to about 210 mg, or about 150 mg to about 200 mg, or about 180 mg to about 270 mg, or about 280 to about 410 mg. The dose is administered at any interval, such as multiple times a week (e.g., twice or three times per week), once a week, once every two weeks, once every three weeks, or once every four weeks. In some or any embodiments, a dose of anti-sclerostin antibody ranging from about 120 mg to about 210 mg is administered once a month. In some or any embodiments, a dose of about 210 mg of the anti-sclerostin antibody is administered once month for 12 months.

[0016] In addition, it may be advantageous to administer multiple doses of an anti-sclerostin antibody or space out the administration of doses, depending on the therapeutic regimen selected for a particular patient. The anti-sclerostin antibody can be administered periodically over a time period of one year or less (e.g., 9 months or less, 6 months or less, or 3 months or less). In this regard, the anti-sclerostin antibody can be administered to the subject once every about 7 days, or 2 weeks, or 3 weeks, or 1 month, or 5 weeks, or 6 weeks, or 7 weeks, or 2 months, or 9 weeks, or 10 weeks, or 11 weeks, or 3 months, or 13 weeks, or 14 weeks, or 15 weeks, or 4 months, or 17 weeks, or 18 weeks, or 19 weeks, or 5 months, or 21 weeks, or 22 weeks, or 23 weeks, or 6 months, or 12 months.

[0017] An “anti-sclerostin antibody” specifically binds to sclerostin or portions thereof to block or impair binding of human sclerostin to one or more ligands. Sclerostin, the product of the SOST gene, is absent in sclerosteosis, a skeletal disease characterized by bone overgrowth and strong dense bones (Brunkow et al., *Am. J. Hum. Genet.*, *68*:577-589

(2001); Balemans et al., *Hum. Mol. Genet.*, *10*:537-543 (2001)). The amino acid sequence of human sclerostin is reported by Brunkow et al. and is disclosed in U.S. Patent Publication No. 20070110747 as SEQ ID NO: 1 (which patent publication is incorporated in its entirety for its description of anti-sclerostin antibodies and Sequence Listing). Recombinant human sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1406-ST-025). Additionally, recombinant mouse sclerostin/SOST is commercially available from R&D Systems (Minneapolis, Minn., USA; 2006 Catalog #1589-ST-025). Research grade sclerostin-binding monoclonal antibodies are commercially available from R&D Systems (Minneapolis, Minn., USA; mouse monoclonal: 2006 Catalog # MAB1406; rat monoclonal: 2006 Catalog # MAB1589). U.S. Patent Nos. 6,395,511 and 6,803,453, and U.S. Patent Publication Nos. 20040009535 and 20050106683 refer to anti-sclerostin antibodies generally. Examples of anti-sclerostin antibodies suitable for use in the context of the invention also are described in U.S. Patent Publication Nos. 20070110747 and 20070072797, which are hereby incorporated by reference. Additional information regarding materials and methods for generating anti-sclerostin antibodies can be found in U.S. Patent Publication No. 20040158045.

[0018] The term "antibody" refers to an intact antibody. An antibody may comprise a complete antibody molecule (including, but not limited to, polyclonal, monoclonal, chimeric, humanized, or human versions having full length heavy and/or light chains). Antibody polypeptides, including fibronectin polypeptide monobodies, also are disclosed in U.S. Patent No. 6,703,199. Other antibody polypeptides are disclosed in U.S. Patent Publication No. 20050238646. Anti-sclerostin antibodies may bind to sclerostin of SEQ ID NO: 1, or a naturally occurring variant thereof, with an affinity of less than or equal to 1×10^{-7}M, less than or equal to 1×10^{-8}M, less than or equal to 1×10^{-9}M, less than or equal to 1×10^{-10}M, less than or equal to 1×10^{-11}M, or less than or equal to 1×10^{-12} M. Affinity may be determined by an affinity ELISA assay. In certain embodiments, affinity may be determined by a BIAcore assay. In certain embodiments, affinity may be determined by a kinetic method. In certain embodiments, affinity may be determined by an equilibrium/solution method.

[0019] Antibody fragments include $F(ab')_2$, Fab, Fab', Fv, Fc, and Fd fragments, and can be incorporated into single domain antibodies, single-chain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, *Nature Biotechnology*, *23*(9):1126-1136 (2005)). An antibody fragment may be any synthetic or genetically engineered protein. For example, antibody fragments include isolated fragments consisting of the light chain variable region, "Fv" fragments consisting of the variable regions of the heavy and light chains, recombinant

single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker (scFv proteins).

[0020] Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs (also termed "minimal recognition units" or "hypervariable region") can be obtained by constructing polynucleotides that encode the CDR of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology, 2*:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies Production, Engineering and Clinical Application*, Ritter et al. (eds.), page 166, Cambridge University Press (1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al., (eds.), page 137, Wiley-Liss, Inc. (1995)).

[0021] In some embodiments, the anti-sclerostin antibody cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747) to sclerostin. Alternatively or in addition, the anti-sclerostin antibody is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747). The terms "cross-block," "cross-blocked," and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to sclerostin. The extent to which an antibody or other binding agent is able to interfere with the binding of another to sclerostin, and therefore whether it can be said to cross-block, can be determined using competition binding assays. In some aspects, a cross-blocking antibody or fragment thereof reduces sclerostin binding of a reference antibody between about 40% and about 100%, such as about 60% and about 100%, specifically between 70% and 100%, and more specifically between 80% and 100%. A particularly suitable quantitative assay for detecting cross-blocking uses a Biacore machine which measures the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between antibodies or other binding agents in terms of their binding to sclerostin.

[0022] Suitable anti-sclerostin antibodies include antibodies described in U.S. Patent Publication No. 20070110747, such as one or more of CDR-H1, CDR-H2, CDR-H3, CDR-

L1, CDR-L2 and CDR-L3 as specifically disclosed therein. At least one of the regions of CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 may have at least one amino acid substitution, provided that the binding agent retains the binding specificity of the non-substituted CDR. The non-CDR portion of the binding agent may be a non-protein molecule, wherein the binding agent cross-blocks the binding of an antibody disclosed herein to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be a non-protein molecule in which the binding agent exhibits a similar binding pattern to human sclerostin peptides in a human sclerostin peptide epitope competition binding assay as that exhibited by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (all of which are described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein or a synthetic peptide, and the recombinant binding protein cross-blocks the binding of an antibody to sclerostin and/or neutralizes sclerostin. The non-CDR portion of the binding agent may be composed of amino acids, wherein the binding agent is a recombinant binding protein, and the recombinant binding protein exhibits a similar binding pattern to human sclerostin peptides in the human sclerostin peptide epitope competition binding assay (described in U.S. Patent Publication No. 20070110747) as that exhibited by at least one of the antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 (described in U.S. Patent Publication No. 20070110747), and/or neutralizes sclerostin. Preferably, the anti-sclerostin antibody is Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, or Ab-24 of U.S. Patent Publication No. 20070110747.

[0023] In addition, the anti-sclerostin antibody can comprise at least one CDR sequence having at least 75% identity (e.g., at least 80%, 90%, or 100% identity) to a CDR selected from SEQ ID NOs: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 78, 79, 80, 81, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 351, 352, 353, 358, 359, and 360 disclosed in U.S. Patent Publication No. 20070110747. Preferably, the anti-sclerostin antibody comprises at least one CDR sequence having at least 75% identity (e.g., at least 80%, 90%, or 100% identity) to a CDR selected from SEQ ID NOs: 245, 246, 247,

78, 79, 80, 269, 270, 271, 239, 240, and 24. In some embodiments, the anti-sclerostin antibody comprises: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

[0024] In some embodiments, the anti-sclerostin antibody comprises at least one CDR sequence having at least 75% (e.g., at least 80%, 90%, or 100% identity) identity to a CDR selected from CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 wherein CDR-H1 has the sequence given in SEQ ID NO: 245 or SEQ ID NO: 269, CDR-H2 has the sequence given in SEQ ID NO: 246 or SEQ ID NO: 270, CDR-H3 has the sequence given in SEQ ID NO: 247 or SEQ ID NO: 271, CDR-L1 has the sequence given in SEQ ID NO: 78 or SEQ ID NO: 239, CDR-L2 has the sequence given in SEQ ID NO: 79 or SEQ ID NO: 240 and CDR-L3 has the sequence given in SEQ ID NO: 80 or SEQ ID NO 241.In some embodiments, the anti-sclerostin antibody comprises a set of 6 CDRS.

[0025] Alternatively, the anti-sclerostin antibody can have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 137 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least

80%, 90%, or 100% identity) to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2 and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 133 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80.

[0026] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 245, 246, and 247, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 141 or a variant thereof in which said CDR's are at least 75% identical to SEQ ID NO: 78, 79, and 80, respectively.

[0027] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 335 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 334 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241, respectively.

[0028] Alternatively, the anti-sclerostin antibody has a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 331 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 330 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241, respectively.

[0029] The anti-sclerostin antibody may have a heavy chain comprising CDR's H1, H2, and H3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 269, 270, and 271, respectively, and a light chain comprising CDR's L1, L2, and L3 and comprising a polypeptide having the sequence provided in SEQ ID NO: 341 or a variant thereof in which said CDR's are at least 75% identical (e.g., at least 80%, 90%, or 100% identity) to SEQ ID NO: 239, 240, and 241.

[0030] Alternatively, the anti-sclerostin antibody has a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 137, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 133; or a heavy chain

comprising a polypeptide having the sequence provided in SEQ ID NO: 145 or 392, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 141; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 335, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 334; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 331, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 330; or a heavy chain comprising a polypeptide having the sequence provided in SEQ ID NO: 345 or 396, and a light chain comprising a polypeptide having the sequence provided in SEQ ID NO: 341.

[0031] In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 145 and a light chain comprising the amino acid sequence set forth in SEQ ID NO: 141.

[0032] Examples of other anti-sclerostin antibodies include, but are not limited to, the anti-sclerostin antibodies disclosed in International Patent Publication Nos. WO 2008/092894, WO 2008/115732, WO 2009/056634, WO 2009/047356, WO 2010/100200, WO 2010/100179, WO 2010/115932, and WO 2010/130830 (each of which is incorporated by reference herein in its entirety).

[0033] It will be understood by one skilled in the art that some proteins, such as antibodies, may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the protein as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperizine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, RJ. *Journal of Chromatography* 705:129-134, 1995).

[0034] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, pp. 79-86 [1983], entirely incorporated by reference), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0035] In some or any embodiments, the C-terminus of the heavy chain of the antibody, comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397), is amidated. In some or any embodiments, both heavy chains of the antibody comprise the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) and both heavy chains are amidated. In some embodiments, the glycine is amidated. Amidation can occur, e.g., as described in Prigg, S.

T. et al., “New insights into copper monooxygenases and peptide amidation: structure, mechanism and function”, Cell. Mol. Life Sci. 57 (2000) 1236–1259. The enzyme peptidylglycine α-amidating monooxygenase (PAM) can catalyze the amidation of glycine. PAM has two active domains, peptidylglycine α-hydroxylating monooxygenase (PHM) and peptidyl-α-hydroxylglycine α-amidating lyase (PAL). PHM catalyzes the conversion of peptidylglycine (along with ascorbate and oxygen) to peptidyl α-hydroxylglycine (along with semidehydrogenascorbate and water). In turn, PAL catalyzes the conversion of peptidyl α-hydroxylglycine to an amidated peptide (and glyoxylate).

[0036] Amidation of an antibody can be controlled by altering certain conditions during the cell culture process. For example, copper (e.g., in ferric ammonium citrate) and/or oxygen levels may be used to influence amidation levels. It is contemplated that increasing copper concentration (e.g., in the media) or oxygen availability (e.g., during culturing) may increase amidation by impacting the activity of an enzyme such as PHM.

[0037] Pharmaceutical Compositions

[0038] In some embodiments, the anti-sclerostin antibody is formulated in a composition together with a pharmaceutically effective diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant. Pharmaceutical compositions of the invention include, but are not limited to, liquid, frozen, and lyophilized compositions.

[0039] In some embodiments, the pharmaceutical composition comprises a population of an anti-sclerostin antibody described herein. For example, in some embodiments, the pharmaceutical composition comprises a mixture of antibodies that specifically bind to sclerostin of SEQ ID NO: 1 and a pharmaceutically acceptable carrier, wherein about 3-5% of the antibodies in the composition are a population of antibodies described herein (e.g., antibodies comprising set of six CDRs set forth in SEQ ID NOs: 78-80 and SEQ ID NOs: 245-247 and having a heavy chain (or two heavy chains) comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) at the C-terminus of the heavy chain(s)). The disclosure also contemplates compositions comprising alternative amounts (e.g., 5-10%, 1-3%, 3-15%, 2-10%, 4-20%, 1-5%) of the population of antibodies described herein (e.g., antibodies comprising set of six CDRs set forth in SEQ ID NOs: 78-80 and SEQ ID NOs: 245-247 and having a heavy chain (or two heavy chains) comprising the amino acid sequence Pro-Ala-Arg-Gly (SEQ ID NO: 397) at the C-terminus of the heavy chain(s)).

[0040] In some embodiments, less than 70% of the antibodies of the population (e.g., about 69%, about 68%, about 67%, about 66%, about 65%, about 64%, about 63%, about 62%, about 61%, about 60%, about 59%, about 58%, about 57%, about 56%, about 55%, about 54%, about 53%, about 52%, about 51%, about 50%, about 49%, about 48%, about 47%, about 46%, about 45%, about 44%, about 43%, about 42%, about 41%, about 40%,

about 39%, about 38%, about 37%, about 36%, about 35%, about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) comprise a heavy chain comprising a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence, which is optionally amidated. In some embodiments, less than 35% (e.g., about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) of the antibodies of the population comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence on both heavy chains, where both heavy chains are optionally amidated. It is also contemplated that both heavy chains comprise the C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence but only one of the chains is amidated. In some embodiments, less than 35% (e.g., about 34%, about 33%, about 32%, about 31%, about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, about 20%, about 19%, about 18%, about 17%, about 16%, about 15%, about 14%, bout 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1% or less) of the antibodies in the composition comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence that is not amidated. In some embodiments, about 33% of antibodies of the population comprise a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence that is amidated, about 33% of the antibodies of the population comprise C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequences on both heavy chains which are both amidated, and about 33% of the antibodies of the population comprise heavy chain(s) with a C-terminal Pro-Ala-Arg-Gly (SEQ ID NO: 397) sequence but which are not amidated.

[0041] In some embodiments, the pharmaceutical composition contains formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In such embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, proline, or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers;

monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. See, REMINGTON'S PHARMACEUTICAL SCIENCES, 18" Edition, (A. R. Genrmo, ed.), 1990, Mack Publishing Company.

[0042] Selection of the particular formulation materials described herein may be driven by, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, supra. The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In specific embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, and may further include sorbitol or a suitable substitute therefor. In certain embodiments, the composition may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in some embodiments, the antibody or fragment may be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0043] The pharmaceutical compositions of the invention can be selected for parenteral delivery. Alternatively, the compositions may be selected for inhalation or for delivery through the digestive tract, such as orally. Preparation of such pharmaceutically acceptable compositions is within the skill of the art. The formulation components are present preferably in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0044] When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antibody or fragment in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antibody or fragment is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antibody or fragment.

[0045] In some or any embodiments, the pharmaceutical composition described herein comprises a calcium salt, an acetate buffer, a polyol and a surfactant. Exemplary calcium salts include, but are not limited to, calcium acetate, calcium carbonate and calcium chloride. In some embodiments, the calcium salt is at a concentration of at least 0.5 mM, at least 1 mM, at least 2 mM, at least 3 mM, at least 4 mM, at least 5 mM, at least 6 mM, at least 7 mM, at least 8 mM, at least 9 mM or at least 10 mM. In certain embodiments, the concentration of calcium salt is not greater than 11 mM, no greater than 12 mM, no greater than 13 mM, no greater than 14 mM, no greater than 15 mM, no greater than 16 mM, no greater than 17 mM, no greater than 18 mM, no greater than 19 mM, no greater than 20 mM, no greater than 21 mM, no greater than 22 mM, no greater than 23 mM, no greater than 24 mM, or no greater than 25 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 0.5 mM to about 10 mM, about 5 mM to about 10 mM, or about 5 mM to about 15 mM.

[0046] In some embodiments, the pharmaceutical composition comprises an acetate buffer (e.g., sodium acetate) having a concentration ranging from about 0.1 mM to about 1000 mM (1 M). In some embodiments, the concentration of the acetate buffer is at least 5 mM, at least 6 mM, at least 7 mM, at least 8 mM, at least 9 mM, at least 10 mM, at least 15 mM, at least 60 mM, at least 70 mM, at least 80 mM, at least 90 mM, at least 100 mM, at least 200 mM, at least 500 mM, at least 700 mM, or at least 900 mM. In some embodiments, the concentration of the acetate buffer is no greater than 10 mM, no greater than 15 mM, no greater than 20 mM, no greater than 25 mM, no greater than 30 mM, no greater than 35 mM, no greater than 40 mM, no greater than 45 mM, no greater than 50 mM, no greater than 55 mM, no greater than 60 mM, no greater than 65 mM, no greater than 70 mM, no greater than 75 mM, no greater than 80 mM, no greater than 85 mM, no greater than 90 mM, no greater than 95 mM or no greater than 100 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to from about 5 mM to about 15 mM, or from about 5 mM to about 10 mM or from about 10 mM to about 25 mM. The buffer is preferably added to a concentration that maintains pH around 5-6 or 5-5.5 or 4.5-5.5. When the calcium salt in the formulation is calcium acetate, in some

embodiments, the total concentration of acetate is about 10 mM to about 55 mM, or about 20 mM to about 40 mM.

[0047] In some aspects, the pharmaceutical composition comprises a total concentration of acetate that is at least about 10 mM, at least about 15 mM, at least about 20 mM, at least about 25 mM, at least about 30 mM, at least about 35 mM, at least about 40 mM, 45 mM, or 50 mM. In some embodiments, the concentration of acetate is no greater than about 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. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 10 mM to about 50 mM, about 20 mM to about 50 mM, about 20 mM to about 40 mM, about 30 mM to about 50 mM, or about 30 mM to about 75 mM. In some embodiments, the calcium salt is calcium acetate and the acetate buffer is sodium acetate. By way of nonlimiting example, a solution containing 10 mM calcium acetate will have 20 mM acetate anion and 10 mM of calcium cation, because of the divalent nature of the calcium cation, while a solution containing 10 mM sodium acetate will have 10 mM sodium cation and 10 mM acetate anion.

[0048] In some embodiments, the total concentration of ions (cations and anions) in solution is at least 10 mM, at least about 15 mM, at least about 20 mM, at least about 25 mM, at least about 30 mM, at least about 35 mM, at least about 40 mM, at least about 45 mM, at least about 50 mM, at least about 55 mM, at least about 60 mM, at least about 65 mM, at least about 70 mM, at least about 75 mM, at least about 80 mM, or at least about 85 mM. In some embodiments, the total concentration of ions is no greater than about 30 mM, no greater than about 35 mM, no greater than about 40 mM, no greater than about 45 mM, no greater than about 50 mM, no greater than about 55 mM, no greater than about 60 mM, no greater than about 65 mM, no greater than about 70 mM, no greater than about 75 mM, no greater than about 80 mM, no greater than about 85 mM, no greater than about 90 mM, no greater than about 95 mM, no greater than about 100 mM, no greater than about 110 mM, no greater than about 120 mM, no greater than about 130 mM, no greater than about 140 mM, no greater than about 150 mM, no greater than about 160 mM, no greater than about 170 mM, no greater than about 180 mM, no greater than about 190 mM or no greater than about 200 mM. Any range featuring a combination of the foregoing endpoints is contemplated, including but not limited to: about 30 mM to about 60 mM, or about 30 mM to about 70 mM, or about 30 mM to about 80 mM, or about 40 mM to about 150 mM, or about 50 mM to about 150 mM. By way of nonlimiting example, a solution of 10 mM calcium acetate will have a 30 mM total concentration of ions (10 mM cations and 20 mM anions).

[0049] In some or any embodiments, the pharmaceutical composition comprises a polyol. Polyols encompass a class of excipients that includes sugars (e.g. mannitol, sucrose, sorbitol) and other polyhydric alcohols (e.g., glycerol and propylene glycol). Exemplary

polyols include, but are not limited to, propylene glycol, glycerin (glycerol), threose, threitol, erythrose, erythritol, ribose, arabinose, arabitol, lyxose, maltitol, sorbitol, sorbose, glucose, mannose, mannitol, levulose, dextrose, maltose, trehalose, fructose, xylitol, inositol, galactose, xylose, fructose, sucrose, 1,2,6-hexanetriol and the like. Higher order sugars include, but are not limited to, dextran, propylene glycol, or polyethylene glycol. Reducing sugars such as fructose, maltose or galactose oxidize more readily than do non-reducing sugars. Additional examples of sugar alcohols are glucitol, maltitol, lactitol or iso-maltulose. Additional exemplary lyoprotectants include glycerin and gelatin, and the sugars mellibiose, melezitose, raffinose, mannotriose, and stachyose. Examples of reducing sugars include glucose, maltose, lactose, maltulose, iso-maltulose and lactulose. Examples of non-reducing sugars include non-reducing glycosides of polyhydroxy compounds selected from sugar alcohols and other straight chain polyalcohols. Monoglycosides include compounds obtained by reduction of disaccharides such as lactose, maltose, lactulose and maltulose.

[0050] In some or any embodiments, the pharmaceutical composition comprises a polyol at a concentration ranging from about 0% to about 40% w/v. In some or any embodiments, the compositions comprise a polyol at concentration of at least 0.5, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 30, or at least 40% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 1, 2, 3, 4, 5, 6, 7, 8, 9% to about 10% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 2% to about 6% w/v. In some or any embodiments, the composition comprises a polyol at a concentration of about 4% w/v. In some or any embodiments, the composition comprises a polyol at about 6% w/v.

[0051] In some or any embodiments, the pharmaceutical composition comprises a surfactant. Exemplary surfactants include, but are not limited to, anionic, cationic, nonionic, zwitterionic, and amphoteric surfactants including surfactants derived from naturally-occurring amino acids. Anionic surfactants include, but are not limited to, sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt. Cationic surfactants include, but are not limited to, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Zwitterionic surfactants include, but are not limited to, CHAPS, CHAPSO, SB3-10, and SB3-12. Non-ionic surfactants include, but are not limited to, digitonin, Triton X-100, Triton X-114, TWEEN-20, and TWEEN-80. In another embodiment, surfactants include, but are not limited to, lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil

10, 40, 50 and 60, glycerol monostearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65 and polysorbate 80, soy lecithin and other phospholipids such as DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. In some or any embodiments, the surfactant is polysorbate 20.

[0052] Surfactants may be included in the compositions either individually or as a mixture in different ratios. In some or any embodiments, the composition comprises a surfactant at a concentration of about 0% to about 5% w/v (e.g., about 0.001, about 0.002, about 0.005, about 0.007, about 0.01, about 0.05, about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1.0, about 1.5, about 2.0, about 2.5, about 3.0, about 3.5, about 4.0, or about 4.5% w/v). In some or any embodiments, the composition comprises a surfactant at a concentration of about 0.001% to about 0.5% w/v. In some or any embodiments, the composition comprises a surfactant at a a concentration of about 0.004, about 0.005, about 0.007, about 0.01, about 0.05, or about 0.1% w/v to about 0.2% w/v. In some or any embodiments, the composition comprises a surfactant at a concentration of about 0.01% to about 0.1% w/v.

[0053] In some or any embodiments, the pharmaceutical composition comprises 55 mM acetate, 13 mm calcium, 6.0 % (w/v) sucrose, 0.006% (w/v) polysorbate 20, pH 5.2.

[0054] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antigen binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which is incorporated by reference and describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3773919 and European Patent Application Publication No. EP058481, each of which is incorporated by reference), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., 1981, supra) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP133988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See, e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692; European Patent Application Publication Nos. EP036676; EP088046 and EP143949, incorporated by reference.

[0055] Pharmaceutical compositions used for *in vivo* administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes. When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0056] The invention is further described in the following example. The example serves only to illustrate the invention and are not intended to limit the scope of the invention in any way.

EXAMPLE

[0057] The following Example describes a multicenter, open-label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to < 12 years of age) and adolescents (12 to < 18 years of age) with OI.

[0058] Romosozumab is a humanized monoclonal antibody immunoglobulin 2 that binds and inhibits sclerostin and has a dual effect on bone of increasing bone formation and decreasing bone resorption. Romosozumab comprises the CDR sequences set forth in SEQ ID NOs: 78-80 and 245-257; light and heavy variable regions set forth in SEQ ID NOs: 376 and 378, respectively; and light and heavy chains set forth in SEQ ID NOs: 141 and 145, respectively.

[0059] Romosozumab is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture in the United States (US EVENITY Prescribing Information), and severe osteoporosis in postmenopausal women at high risk for fracture in European Union (EU EVENITY Summary of Product Characteristics).

[0060] Proof of biological activity for romosozumab was established in a first-in-human, ascending single-dose study in healthy males and postmenopausal females, an ascending multiple dose study in healthy males and postmenopausal females with low bone mass and in a phase 2 dose-ranging study in postmenopausal females with low bone mass. In all studies, treatment with romosozumab was generally well tolerated and resulted in a transient increase of the bone formation markers procollagen type I N-terminal propeptide (P1NP), osteocalcin, and bone-specific alkaline phosphatase, and a decrease in the bone resorption marker serum type I collagen C-telopeptide (sCTX) (McClung et al, 2014; Padhi et al, 2014; Padhi et al, 2011). With gains in bone mass, the risk for patients to experience an osteoporotic fracture can be lessened, as demonstrated during the romosozumab phase 3 programs. In this phase 1b, open-label, ascending multiple dose study, the safety,

tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of romosozumab were evaluated in children and adolescents with OI."

[0061] All subjects received 3 subcutaneous (SC) doses of romosozumab every 4 weeks (QM). Subjects in cohort 1 (12 to <18 years of age) and cohort 2 (5 to < 12 years of age) were administered romosozumab 1 mg/kg SC QM. Subjects in cohort 3 (12 to < 18 years of age) and cohort 4 (5 to < 12 years of age) were administered romosozumab 3 mg/kg SC QM. Subjects in cohort 5 (12 to < 18 years of age) and cohort 6 (5 to < 12 years of age) were administered romosozumab 5 mg/kg SC QM. All subjects received daily supplementation with calcium and vitamin D.

[0062] Key Baseline demographics and Characteristics are provided below in Table 1.

	Cohort 1 1 mg/kg (n=4)	Cohort 2 1 mg/kg (n=4)	Cohort 3 3 mg/kg (n=4)	Cohort 4 3 mg/kg (n=5)	Cohort 5 5 mg/kg (n=4)	Cohort 6 5 mg/kg (n=4)	Overall (n=25)
Male n (5)	3 (75)	4 (100)	3 (75)	1 (20)	2 (50)	3 (75)	16 (64)
Mean age (years)	14.3	6	14.3	8.4	14	6.5	10.5
Mean body weight (kg)	55.9	19.5	66	26.7	43.6	16.9	37.6
Mean BMI	21.2	15.6	24.1	17.4	23.8	15.5	19.5
Mean lumbar spine BMD (g/cm^2)	0.69	0.35	0.60	0.49	0.74	0.35	0.54
Mean lumbar spine BMP Z-score	-2.43	-3.08	-2.95	-1.9	-1.65	-2.6	-2.57
Type of OI n (%)							
I	3 (75)	3 (75)	3 (75)	1 (20)	2 (50)	2 (50)	14 (56)
II	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
III	0 (0)	1 (25)	1 (25)	4 (80)	2 (50)	2 (50)	10 (40)
IV	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Facture history n (%)							
Yes	4 (100)	4 (100)	4 (100)	5 (100)	4 (100)	4 (100)	25 (100)
Nonveretebral	2 (50)	4 (100)	4 (100)	5 (100)	4 (100)	3 (75)	22 (88)

[0063] Results:

[0064] Twelve of 25 subjects (48.0%) had treatment-emergent adverse events during the study. Serious treatment-emergent adverse events were reported for 2 subjects (8.0%); these events included femur fracture and lower limb fracture. None of these events were considered related to the investigational product by the investigator. The overall study results show that romosozumab was well tolerated in the pediatric population with OI.

[0065] As shown in Figure 1, romosozumab exhibited nonlinear PK at lower doses of 1 and 3 mg/kg across both ae groups. The PK approached linearity at 5 mg/kg.

[0066] As shown in Figure 2, Pharmacokinetics (PK) in pediatric OI subjects was non-linear between 1 and 3 mg/kg, as seen in adults; PK approaches linearity at 5mg/kg.

[0067] A trend of dose-related increases was observed in P1NP, lumbar spine BMD, and BMD Z-score values in both adolescents and children.

[0068] There appeared to be a dose response in elevation of the P1NP levels in both adolescents and children. P1NP levels increased when measured after dosing (on days 8 to 15). The mean percentage change in P1NP levels from baseline ranged from 11.03% to 58.58% at day 15 for the adolescents and from 10.52% to 28.35% at day 15 for the children. P1NP levels returned towards the baseline until next dosing. P1NP levels returned close to baseline by day 113 in both adolescents and children. See Figures 2A and 2B.

[0069] CV% of exposure parameters tend to be lower in 5 mg/kg cohorts relative to lower doses cohorts. Minimal accumulation was observed between the first and third doses, the mean accumulation ratios were generally less than 1. See Figures 3A and 3B.

[0070] Figures 4A and 4B show that there was a trend of dose-related changes in lumbar spine BMC with increase in mean percentage change from baseline ranging from 7.68% to 18.16% at day 85 and from 12.64% to 21.29% at day 169 for the adolescents, and from 8.41% to 16.03% at day 85 and from 7.98% to 12.42% at day 169 for the children.

[0071] Figures 5A and 5B show that most subjects, both adolescents and children, also showed increased lumbar spine BMD Z-scores after 3 monthly doses of romosozumab, with increase in mean BMD Z-scores from baseline ranging from 0.20 to 0.50 at day 85 and from 0.23 to 0.48 at day 169 in the adolescents, and from 0.33 to 0.53 at day 85 and from 0.25 to 0.50 at day 169 in the children.

[0072] All of the references cited herein, including patents, patent applications, literature publications, and the like, are hereby incorporated in their entireties by reference.

[0073] While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred compounds and methods may be used and that it is intended that the invention

may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WHAT IS CLAIMED IS:

1. A method for treating osteogenesis imperfecta (OI) in a subject, the method comprising administering to the subject an anti-sclerostin antibody in an amount from about 1 mg/kg to about 10 mg/kg, wherein the subject is less than 17 years of age.

2. The method of claim 1, comprising administering 1 mg/kg anti-sclerostin antibody to the subject.

3. The method of claim 1, comprising administering 3 mg/kg anti-sclerostin antibody to the subject.

4. The method of claim 1, comprising administering 5 mg/kg anti-sclerostin antibody to the subject.

5. The method of any one of claims 1-4, wherein an amount of the antibody is administered to the subject once a month.

6. The method of any one of claims 1-5, comprising administering 210 mg anti-sclerostin antibody to the subject.

7. The method of any one of claims 1-6, where the antibody cross-blocks the binding of at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24 to sclerostin.

8. The method of any one of claims 1-7, wherein the antibody is cross-blocked from binding to sclerostin by at least one of antibodies Ab-A, Ab-B, Ab-C, Ab-D, Ab-1, Ab-2, Ab-3, Ab-4, Ab-5, Ab-6, Ab-7, Ab-8, Ab-9, Ab-10, Ab-11, Ab-12, Ab-13, Ab-14, Ab-15, Ab-16, Ab-17, Ab-18, Ab-19, Ab-20, Ab-21, Ab-22, Ab-23, and Ab-24.

9. The method of any one of claim 1-8, wherein the antibody comprises: a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs:45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID

NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271; r) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; or s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

10. The method of claim 9, wherein the antibody comprises CDRH-1, CDR-H2, CDR-H3, CDR-L1 CDR-L2 and CDR-L3 wherein (a) CDR-H1 is SEQ ID NO:245, CDR-H2 is SEQ ID NO:246, CDR-H3 is SEQ ID NO:247, CDR-L1 is SEQ ID NO:78, CDR-L2 is SEQ ID NO:79 and CDR-L3 is SEQ ID NO:80; or (b) CDR-H1 is SEQ ID NO:269, CDR-H2 is SEQ ID NO:270, CDR-H3 is SEQ ID NO:271, CDR-L1 is SEQ ID NO:239, CDR-L2 is SEQ ID NO:240 and CDR-L3 is SEQ ID NO:241.

11. The method of any one of claims 1-10, wherein the antibody is a human antibody, a humanized antibody, a monoclonal antibody, or a chimeric antibody.

12. The method of any one of claims 1-11 further comprising administering vitamin D to the subject.

13. Use of an anti-sclerostin antibody in preparation of a medicament for treating osteogenesis imperfecta in a subject in an amount from about 1 mg/kg to about 10 mg/kg, wherein the wherein the subject is less than 17 years of age.