

COMPOSITIONS, DOSES, AND METHODS FOR TREATMENT OF THYROID EYE DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/611,151, filed December 17, 2023, U.S. Provisional Application No. 63/656,371, filed June 5, 2024, and U.S. Provisional Application No. 63/696,278, filed September 18, 2024, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Thyroid-associated ophthalmopathy (TAO), also known as thyroid eye disease (TED), Graves' ophthalmopathy or orbitopathy (GO), thyrotoxic exophthalmos, dysthyroid ophthalmopathy, and several other terms, is orbitopathy associated with thyroid dysfunction. TAO is divided into two types. Active TAO (also known as acute TAO), which typically lasts 1-3 years, is characterized by an ongoing autoimmune/inflammatory response in the soft tissues of the orbit. Active TAO is responsible for the expansion and remodeling of the ocular soft tissues. The autoimmune/inflammatory response of active TAO spontaneously resolves and the condition transitions into inactive TAO. Inactive TAO (also known as chronic TAO) is the term used to describe the long-term/permanent sequelae of active TAO. The cause of TAO is unknown. TAO is typically associated with Graves' hyperthyroidism, but can also occur as part of other autoimmune conditions that affect the thyroid gland and produce pathology in orbital and periorbital tissue, and, rarely, the pretibial skin (pretibial myxedema) or digits (thyroid acropachy). TAO is an autoimmune orbitopathy in which the orbital and periocular soft tissues are primarily affected with secondary effects on the eye and vision. In TAO, as a result of inflammation and expansion of orbital soft tissues, primarily eye muscles and adipose, the eyes are forced forward (bulge) out of their sockets--a phenomenon termed proptosis or exophthalmos. Although most cases of TAO do not result in loss of vision, this condition can cause vision-threatening exposure keratopathy, troublesome diplopia (double vision), and compressive dysthyroid optic neuropathy. TAO may precede, coincide with, or follow the systemic complications of dysthyroidism. The ocular manifestations of TAO include upper eyelid retraction, lid lag, swelling, redness (erythema), conjunctivitis, and bulging eyes (exophthalmos or proptosis), chemosis, periorbital edema, and altered ocular motility with significant functional, social, and cosmetic consequences. Many of the signs and symptoms of

TAO, including proptosis and ocular congestion, result from expansion of the orbital adipose tissue and periocular muscles. The adipose tissue volume increases owing in part to new fat cell development (adipogenesis) within the orbital fat. The accumulation of hydrophilic glycosaminoglycans, primarily hyaluronic acid, within the orbital adipose tissue and the perimysial connective tissue between the extraocular muscle fibers, further expands the fat compartments and enlarges the extraocular muscle bodies. Hyaluronic acid is produced by fibroblasts residing within the orbital fat and extraocular muscles, and its synthesis in vitro is stimulated by several cytokines and growth factors, including IL-1 β , interferon- γ , platelet-derived growth factor, thyroid stimulating hormone (TSH) and insulin-like growth factor I (IGF-I).

[0003] Antibodies that activate the insulin-like growth factor I receptor (IGF-IR) have also been detected and implicated in active TAO. Without being bound to any theory, it is believed that TSHR and IGF-IR form a physical and functional complex in orbital fibroblasts, and that blocking IGF-IR appears to attenuate both IGF-1 and TSH-dependent signaling. It has been suggested that blocking IGF-IR using an antibody antagonist might reduce both TSHR- and IGF-I-dependent signaling and therefore interrupt the pathological activities of autoantibodies acting as agonists on either receptor.

[0004] IGF-IR is a widely expressed heterotetrameric protein involved in the regulation of proliferation and metabolic function of many cell types. It is a tyrosine kinase receptor comprising two subunits. IGF-IR α contains a ligand-binding domain while IGF-IR β is involved in signaling and contains tyrosine kinase and tyrosine phosphorylation sites.

[0005] Current therapies for hyperthyroidism due to Graves' disease are imperfect because therapies targeting the specific underlying pathogenic autoimmune mechanisms of the disease are lacking. Even more complex is the treatment of moderate-to-severe active TAO. Although recent years have witnessed a better understanding of its pathogenesis, TAO remains a therapeutic challenge and dilemma. There are no approved drugs to treat active TAO. Intravenous glucocorticoids (ivGCs) and oral glucocorticoids are used to treat patients with moderate-to-severe active TAO, but results are seldom satisfactory. Partial responses are frequent and relapses (rebound) after drug withdrawal are not uncommon. Adverse events do occur and many patients eventually require rehabilitative surgery conducted when their condition has transitioned to inactive TAO. Accordingly, there is still a need to provide alternative therapies for TAO and its related symptoms.

SUMMARY

[0006] The disclosure relates generally to IGF-1R antibodies, and antigen binding fragments thereof and uses thereof. Certain IGF-1R antibodies and antigen-binding fragments inhibit IGF-1R function or block the biological functions of IGF-I mediated IGF-1R signaling. Additionally, the invention generally relates to methods for treating thyroid-associated ophthalmopathy (TAO), also known as thyroid eye disease (TED), Graves' ophthalmopathy or orbitopathy (GO), thyrotoxic exophthalmos, dysthyroid ophthalmopathy, and other thyroid eye disorders associated with IGF-1R signaling.

[0007] In some embodiments, methods of treating thyroid eye disease in a subject are provided. In some embodiments, the methods comprise administering to the subject subcutaneously a pharmaceutical composition comprising a therapeutically effective amount of an anti-IGF-1R antibody.

[0008] In some embodiments, the therapeutically effective amount comprises 300 mg or 600 mg of the antibody. In some embodiments, the antibody is as provided herein, such as, but not limited to, VRDN-003. In some embodiments, the antibody is as provided herein, such as, but not limited to, VRDN-001. In some embodiments, the antibody is as provided herein, such as, but not limited to, VRDN-002.

[0009] The present invention provides, among other things, a safer and more potent method for treating thyroid eye disease (TED) based on VRDN-003 and other anti-IGF-1R antibodies using dosing regimens described herein. The present invention is, in part, based on the more therapeutically effective dosing regimen, which comprises subcutaneously administering an anti-IGF-1R antibody with an initial loading dose of between 400 mg and 800 mg followed by at least maintenance dose of between 200 mg and 400 mg no more frequently than every 3 weeks.

[0010] In one aspect, the present invention provides, among other things, a method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a therapeutically effective amount of an anti-IGF-1R antibody, wherein the therapeutically effective amount is 200 mg to 700 mg of the anti-IGF-1R antibody, and wherein the antibody comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, a LCDR3 of SEQ ID NO: 3, a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.

[0011] In some embodiments, the therapeutically effective amount is 250 to 650 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 300 to

600 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 200 to 400 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 500 to 700 mg of the anti-IGF-1R antibody.

[0012] In some embodiments, the therapeutically effective amount is 200 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 250 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 300 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 350 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 400 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 450 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 500 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 550 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 600 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 650 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 700 mg of the anti-IGF-1R antibody.

[0013] In some embodiments, the method comprises administering an initial loading dose and at least one maintenance dose.

[0014] In some embodiments, the at least one maintenance dose is administered 2 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 3 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 4 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 5 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 6 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 7 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 8 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 9 weeks following the initial loading dose. In some embodiments, the at least one maintenance dose is administered 10 weeks following the initial loading dose.

[0015] In some embodiments, the initial loading dose is higher than the at least one maintenance dose.

[0016] In some embodiments, the initial loading dose administered to the subject is 400 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 500 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 600 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 700 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 500 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 500 mg to 700 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 500 mg to 600 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 600 mg to 800 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 600 mg to 700 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 550 mg to 650 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 575 mg to 625 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 585 mg to 615 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 595 mg to 605 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 575 mg to 625 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 585 mg to 615 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 595 mg to 605 mg of the anti-IGF-1R antibody.

[0017] In some embodiments, the initial loading dose administered to the subject is 590 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 595 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 600 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 605 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administered to the subject is 610 mg of the anti-IGF-1R antibody.

[0018] In some embodiments, the maintenance dose is 100 mg to 500 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 100 mg to 400 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 100 mg to 300 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 100 mg to 200 mg

of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 100 mg to 400 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 200 mg to 500 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 200 mg to 400 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 200 mg to 300 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 300 mg to 500 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 300 mg to 400 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 250 mg to 350 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 275 mg to 325 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 285 mg to 315 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 100 mg, 200 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 275 mg, 285 mg of the anti-IGF-1R antibody.

[0019] In some embodiments, the maintenance dose is 290 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 295 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 300 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 305 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 310 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 315 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 325 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 400 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 500 mg of the anti-IGF-1R antibody.

[0020] In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 5 µg/ml in the subject. In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 8 µg/ml in the subject. In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 10 µg/ml in the subject. In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 12 µg/ml in the subject. In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 15 µg/ml in the subject. In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 20 µg/ml in the subject.

[0021] In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 1 week. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 2 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 3 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 4 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 5 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 6 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 7 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 8 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 9 weeks. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at least 10 weeks.

[0022] In one aspect, the present invention provides, among other things, a method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a therapeutically effective amount of an anti-IGF-1R antibody, wherein the therapeutically effective amount comprises an initial dose of 600 mg and at least one maintenance dose of 300 mg, wherein the antibody comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, a LCDR3 of SEQ ID NO: 3, a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.

[0023] In some embodiments, the anti-IGF-1R antibody is administered every week. In some embodiments, the anti-IGF-1R antibody is administered every 2 weeks. In some embodiments, the anti-IGF-1R antibody is administered every 4 weeks. In some embodiments, the anti-IGF-1R antibody is administered every 8 weeks. In some embodiments, the anti-IGF-1R antibody is administered every 10 weeks. In some embodiments, the anti-IGF-1R antibody is administered every 12 weeks. In some embodiments, the anti-IGF-1R antibody is administered every 16 weeks. In some embodiments, the anti-IGF-1R antibody is administered once a month. In some embodiments, the anti-IGF-1R antibody is administered once every 2 months. In some embodiments, the anti-IGF-1R antibody is administered once every 3 months. In some embodiments, the anti-IGF-1R antibody is administered once every 4 months.

[0024] In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 2 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 3 weeks. In some embodiments, the anti-

IGF-1R antibody is administered no more frequently than once every 4 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 5 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 6 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 8 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 10 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 12 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 15 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 16 weeks. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every month. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 2 months. In some embodiments, the anti-IGF-1R antibody is administered no more frequently than once every 4 months.

[0025] In some embodiments, the total number of doses administered to the subject is 2 doses. In some embodiments, the total number of doses administered to the subject is 3 doses. In some embodiments, the total number of doses administered to the subject is 4 doses. In some embodiments, the total number of doses administered to the subject is 5 doses. In some embodiments, the total number of doses administered to the subject is 6 doses. In some embodiments, the total number of doses administered to the subject is 7 doses. In some embodiments, the total number of doses administered to the subject is 8 doses. In some embodiments, the total number of doses administered to the subject is 9. In some embodiments, the total number of doses administered to the subject is 10 doses. In some embodiments, the total number of doses administered to the subject is 11 doses. In some embodiments, the total number of doses administered to the subject is 12 doses.

[0026] In some embodiments, the thyroid eye disease is acute thyroid eye disease. In some embodiments, the thyroid eye disease is active thyroid eye disease. In some embodiments, the thyroid eye disease is chronic thyroid eye disease.

[0027] In some embodiments, the subject with chronic thyroid eye disease prior to administration of the first dose has had a clinical diagnosis of TED with any CAS (0-7). In some embodiments, the subject with chronic thyroid eye disease prior to administration of the first dose has had moderate to severe chronic TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender. In some embodiments, the subject with chronic thyroid eye disease prior to administration of the first

dose has had proptosis of ≥ 17 mm in the study eye as measured by exophthalmometer or MRI/CT. In some embodiments, the subject with chronic thyroid eye disease prior to administration of the first dose has had ocular symptoms or signs associated with chronic TED that began > 15 months prior to study.

[0028] In some embodiments, the subject with active thyroid eye disease prior to administration of the first dose has had ocular symptoms or signs associated with active TED that began within 15 months prior to study screening. In some embodiments, the subject with active thyroid eye disease prior to administration of the first dose has had a clinical diagnosis of TED with a CAS of ≥ 3 . In some embodiments, the subject with active thyroid eye disease prior to administration of the first dose has had moderate to severe active TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender. In some embodiments, the subject with active thyroid eye disease prior to administration of the first dose has had proptosis of ≥ 17 mm in the study eye as measured by exophthalmometer. In some embodiments, the subject with active thyroid eye disease prior to administration of the first dose has had one or more of the following symptoms: lid retraction of ≥ 2 mm, moderate or severe soft tissue involvement, inconstant or constant diplopia, spontaneous retrobulbar pain or pain on eye movement, swelling of the conjunctiva, eyelids or plica, or redness of the eyelids or plica in the study eye.

[0029] In some embodiments, wherein the subject with chronic thyroid eye disease prior to administration of the first dose has had symptoms of thyroid eye disease for at least, or greater than, one year and has one or more of the following symptoms: lid retraction greater than 2 mm, exophthalmos (proptosis) of greater than or equal to 3 mm, Clinical Activity Score (CAS) from 0 to 7, and inconstant or constant diplopia.

[0030] In some embodiments, the subject has proptosis greater than or equal to 3 mm above the normal range for their race and gender.

[0031] In some embodiments, the subject has a CAS from 0 to 7. In some embodiments, the subject has a CAS greater than 1. In some embodiments, the subject has a CAS greater than 2. In some embodiments, the subject has a CAS greater than 3. In some embodiments, the subject has a CAS greater than 4. In some embodiments, the subject has a CAS greater than 5. In some embodiments, the subject has a CAS greater than 6.

[0032] In some embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of greater than 0. In some embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of greater than 1. In some

embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of greater than 2. In some embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of greater than 3. In some embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of greater than 4. In some embodiments, wherein the subject, prior to administration of the anti-IGF-1R antibody, had a CAS of between 2 and 4.

[0033] In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 2 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 3 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 4 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 5 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 6 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 6 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 5 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 4 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 3 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 2 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 6 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 5 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 4 years. In some embodiments, the patient, prior to administration of the first dose, has had

symptoms of thyroid eye disease for 2 to 3 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 to 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 to 5 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 to 4 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 4 to 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 4 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 4 to 6 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 4 to 5 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 5 to 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 5 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 5 to 6 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 6 to about 8 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 6 to 7 years. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 7 to 8 years.

[0034] In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 63 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 60 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 48 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 36 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 24 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 12 months.

[0035] In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 15 months. In some embodiments, the patient,

prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 to 13 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 10 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 12 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 to 12 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 5 to 10 months.

[0036] In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 month. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 2 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 3 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 4 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 5 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 6 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 7 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 8 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 9 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 10 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 11 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 12 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 13 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 14 months. In some embodiments, the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 15 months.

[0037] In some embodiments, the patient does not have any hearing impairment after administration of the anti-IGF-1R antibody. In some embodiments, the patient does not have any ototoxic changes in audiometry after administration of the anti-IGF-1R antibody. In some

embodiments, the patient does not have any hyperglycemic events after administration of the anti-IGF-1R antibody.

[0038] In some embodiments, the treated subject's proptosis is reduced by at least 1 nm. In some embodiments, the treated subject's proptosis is reduced by at least 2 nm. In some embodiments, the treated subject's proptosis is reduced by at least 3 nm. In some embodiments, the treated subject's proptosis is reduced by at least 4 nm. In some embodiments, the treated subject's proptosis is reduced by at least 5 nm. In some embodiments, the treated subject's proptosis is reduced by 1-4 mm. In some embodiments, the treated subject's proptosis is reduced by 2-3 mm.

[0039] In some embodiments, the proptosis is reduced within 2 weeks of the first dose. In some embodiments, the proptosis is reduced within 3 weeks of the first dose. In some embodiments, the proptosis is reduced within 4 weeks of the first dose. In some embodiments, the proptosis is reduced within 5 weeks of the first dose. In some embodiments, the proptosis is reduced within 6 weeks of the first dose. In some embodiments, the proptosis is reduced within 8 weeks of the first dose. In some embodiments, the proptosis is reduced within 10 weeks of the first dose. In some embodiments, the proptosis is reduced within 12 weeks of the first dose.

[0040] In some embodiments, the treated subject has reduced diplopia.

[0041] In some embodiments, wherein the diplopia is resolved in the treated subject, (i.e., complete resolution of diplopia). In some embodiments, wherein the subject has complete resolution of diplopia post treatment.

[0042] In some embodiments, the diplopia is reduced within 2 weeks of the first dose. In some embodiments, the diplopia is reduced within 3 weeks of the first dose. In some embodiments, the diplopia is reduced within 4 weeks of the first dose. In some embodiments, the diplopia is reduced within 5 weeks of the first dose. In some embodiments, the diplopia is reduced within 6 weeks of the first dose. In some embodiments, the diplopia is reduced within 3 weeks of the first dose. In some embodiments, the diplopia is reduced within 8 weeks of the first dose. In some embodiments, the diplopia is reduced within 10 weeks of the first dose. In some embodiments, the diplopia is reduced within 12 weeks of the first dose.

[0043] In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 2 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 3 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 4 weeks. In some embodiments, the

subject has an improvement in Clinical Activity Score (CAS) within 5 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 6 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 8 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 10 weeks. In some embodiments, the subject has an improvement in Clinical Activity Score (CAS) within 12 weeks.

[0044] In some embodiments, the CAS score has an improvement of at least -1. In some embodiments, the CAS score has an improvement of at least -2. In some embodiments, the CAS score has an improvement of at least -3. In some embodiments, the CAS score has an improvement of at least -2. In some embodiments, the CAS score has an improvement of at least -4. In some embodiments, the CAS score has an improvement of at least -5.

[0045] In some embodiments, the subject has no worsening of Clinical Activity Score (CAS) post treatment.

[0046] In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 2 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 3 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 4 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 5 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 6 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 8 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 10 weeks of the first dose. In some embodiments, the subject has a reduction in proptosis and an improvement in CAS score within 12 weeks of the first dose.

[0047] In some embodiments, the proptosis is reduced by 1 to 3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry. In some embodiments, the proptosis is reduced by 1 to 2 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry. In some embodiments, the proptosis is reduced by 2 to 3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry.

[0048] In some embodiments, the proptosis is reduced by 1 to 3 mm from baseline within 6 weeks of the first dose as measured by MRI/CT. In some embodiments, the proptosis is reduced by 1 to 2 mm from baseline within 6 weeks of the first dose as measured by

MRI/CT. In some embodiments, the proptosis is reduced by 2 to 3 mm from baseline within 6 weeks of the first dose as measured by MRI/CT.

[0049] In some embodiments, after first dose of the antibody, the clinical activity score of the subject is reduced. In some embodiments, after two doses of the antibody, the clinical activity score of the subject is reduced. In some embodiments, after three doses of the antibody, the clinical activity score of the subject is reduced. In some embodiments, after four doses of the antibody, the clinical activity score of the subject is reduced.

[0050] In some embodiments, the patient with chronic TED exhibits fibrosis.

[0051] In some embodiments, the administration of the anti-IGF-1R antibody results in the treatment of fibrosis.

[0052] In some embodiments, fibrosis is reduced post-treatment with an anti-IGF-1R antibody. In some embodiments, fibrosis is alleviated post-treatment with an anti-IGF-1R antibody. In some embodiments, fibrosis is reversed post-treatment with an anti-IGF-1R antibody.

[0053] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7. In some embodiments, a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[0054] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[0055] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[0056] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[0057] In some embodiments, the antibody comprises a LCDR1 of SEQ ID NO: 12, a LCDR2 of SEQ ID NO: 13, a LCDR3 of SEQ ID NO: 14, a HCDR1 of SEQ ID NO: 15, a HCDR2 of SEQ ID NO: 16 and a HCDR3 of SEQ ID NO: 17.

[0058] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

[0059] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

[0060] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 21.

[0061] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 21.

[0062] In some embodiments, the antibody comprises a LCDR1 of SEQ ID NO: 22, a LCDR2 of SEQ ID NO: 23, a LCDR3 of SEQ ID NO: 24, a HCDR1 of SEQ ID NO: 25, a HCDR2 of SEQ ID NO: 26 and a HCDR3 of SEQ ID NO: 27.

[0063] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

[0064] In some embodiments, a light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

[0065] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 31.

[0066] In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 31.

[0067] In some embodiments, the Fc region of the heavy chain comprises the mutations M252Y, S254T, and T256E, according to EU numbering. In some embodiments, the Fc region of the heavy chain comprises the mutations M428L, and N434S, according to EU numbering.

[0068] In one aspect, the present invention provides, among other things, a method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously an anti-IGF-1R antibody at a dose amount of 300 mg or 600 mg no more than once every 4 weeks, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[0069] In some embodiments, the anti-IGF-1R antibody is administered at a dose amount of 300 mg. In some embodiments, the anti-IGF-1R antibody is administered at a dose amount of 600 mg.

[0070] In some embodiments, the anti-IGF-1R antibody is administered at once every 4 weeks. In some embodiments, the anti-IGF-1R antibody is administered at once every 6 weeks. In some embodiments, the anti-IGF-1R antibody is administered at once every 8 weeks.

[0071] In some embodiments, the method further comprises administering magnesium to the subject. In some embodiments, the magnesium is administered prior to the administration of the anti-IGF-1R antibody. In some embodiments, the magnesium is administered during the administration of the anti-IGF-1R antibody. In some embodiments, the magnesium is administered after the administration of the anti-IGF-1R antibody. In some embodiments, the magnesium is administered 1-2 days prior to subsequent administration of the anti-IGF-1R antibody.

[0072] In some embodiments, the magnesium is administered at a dose of 100-1000 mg. In some embodiments, the magnesium is administered at a dose of 200-800 mg. In some embodiments, the magnesium is administered at a dose of 200-600 mg. In some embodiments, the magnesium is administered at a dose of 300-500 mg. In some embodiments, the magnesium is administered at a dose of 300 mg. In some embodiments, the magnesium is administered at a dose of 400 mg. In some embodiments, the magnesium is administered at a dose of 500 mg. In some embodiments, the magnesium is administered orally.

BRIEF DESCRIPTION OF THE DRAWINGS

[0073] The drawings herein are for illustrative purposes only and should not be limiting.

[0074] **FIG. 1** is an exemplary graph of showing concentration of anti-IGF-1R antibody after administration over time.

[0075] FIG. 2 is an exemplary graph of showing fold change from baseline of IGF-1 after administration over time.

[0076] FIG. 3A is an exemplary graph of showing comparing drug concentration post administration of 300 mg VRDN-003 Q4W SC as compared to 3 mg/kg VRDN-001 IV. FIG. 3B is an exemplary graph of showing comparing drug concentration post administration of 300 mg VRDN-003 Q4W SC as compared to 10 mg/kg VRDN-001 IV.

[0077] FIG. 4 is an exemplary graph of showing comparing drug concentration post administration of 300 mg VRDN-003 Q8W SC as compared to 3 mg/kg VRDN-001 IV.

[0078] FIG. 5 is an exemplary graph of showing comparing drug concentration post administration of 300 mg VRDN-003 Q2W SC as compared to 10 mg/kg VRDN-001 IV.

[0079] FIG. 6 is an exemplary bar graphs showing Cmin and Cmax of different dosing regimen disclosed in the present application.

[0080] FIG. 7A is a series of exemplary graphs showing serum concentration or level of IGF-1 post IV administration of VRDN-002. FIG. 7B is a series of exemplary graphs showing serum concentration or level of IGF-1 post IV or SC administration of VRDN-002.

DETAILED DESCRIPTION

[0081] Provided herein are antibodies that bind and modulate the activity of IGF-1R. The antibodies can be used, for example, to treat thyroid eye disease.

[0082] Any numerical values used in this application are meant to cover any variations within the standard deviation or normal fluctuations appreciated by one of ordinary skill in the relevant art.

[0083] As used herein, "Thyroid-associated Ophthalmopathy" (TAO), "Thyroid Eye Disease" (TED), "Graves' Ophthalmopathy" or "Graves' Orbitopathy" (GO) refer to the same disorder or condition and are used interchangeably. They all refer to the inflammatory orbital pathology associated with some autoimmune thyroid disorders, most commonly with "Graves' Disease" (GD), but sometimes with other diseases, e.g. Hashimoto's thyroiditis.

[0084] The terms "proptosis" and "exophthalmos" (also known as exophthalmus, exophthalmia, or exorbitism) refer to the forward projection, displacement, bulging, or protrusion of an organ. As used herein, the terms refer to the forward projection, displacement, bulging, or protrusion of the eye anteriorly out of the orbit. Proptosis and exophthalmos are considered by some of skill in the art to have the same meaning and are often used

interchangeably, while others attribute subtle differences to their meanings. Exophthalmos is used by some to refer to severe proptosis; or to refer to endocrine-related proptosis. Yet others use the term exophthalmos when describing proptosis associated with the eye, in, for example, subjects with TAO (TED or GO).

[0085] As used herein, the terms "proptosis" and "exophthalmos" are used interchangeably and refer to the forward projection, displacement, bulging, or protrusion of the eye anteriorly out of the orbit. Owing to the rigid bony structure of the orbit with only anterior opening for expansion, any increase in orbital soft tissue contents taking place from the side or from behind will displace the eyeball forward. Proptosis or exophthalmos can be the result of a several disease processes including infections, inflammations, tumors, trauma, metastases, endocrine lesions, vascular diseases & extra orbital lesions. TAO (TED or GO) is currently recognized as the most common cause of proptosis in adults. Exophthalmos can be either bilateral, as is often seen in TAO (TED or GO), or unilateral (as is often seen in an orbital tumor).

[0086] Measurement of the degree of exophthalmos can be performed using, for example, an exophthalmometer, an instrument used for measuring the degree of forward displacement of the eye. The device allows measurement of the forward distance of the lateral orbital rim to the front of the cornea. Computed tomography (CT) scanning and Magnetic resonance imaging (MRI) may also be used in evaluating the degree of exophthalmos or proptosis. CT scanning is an excellent imaging modality for the diagnosis of TAO. In addition to allowing visualization of the enlarged extraocular muscles, CT scans provide the surgeon or clinician with depictions of the bony anatomy of the orbit when an orbital decompression is required. MRI, with its multi-planar and inherent contrast capabilities, provides excellent imaging of the orbital contents without the radiation exposure associated with CT scan studies. MRI provides better imaging of the optic nerve, orbital fat, and extraocular muscle, but CT scans provide better views of the bony architecture of the orbit. Orbital ultrasonography can also be used for the diagnosis and evaluation of TAO, because it can be performed quickly and with a high degree of confidence. High reflectivity and enlargement of the extraocular muscles are assessed easily, and serial ultrasonographic examinations can also be used to assess progression or stability of the ophthalmopathy. Based on the technologies currently available, or that will become available in the future, one of skill in the art would be capable of determining the best modality for diagnosing and evaluating the extent of proptosis or exophthalmos.

[0087] As used herein, the term “antibody” refers to any form of antibody that exhibits the desired biological activity. Thus, it is used in the broadest sense and specifically covers, but is not limited to, monoclonal antibodies (including full length monoclonal antibodies), polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), humanized, fully human antibodies, chimeric antibodies and camelized single domain antibodies. “Parental antibodies” are antibodies obtained by exposure of an immune system to an antigen prior to modification of the antibodies for an intended use, such as humanization of an antibody for use as a human therapeutic antibody.

[0088] As used herein, unless otherwise indicated, “antibody fragment” or “antigen binding fragment” refers to antigen binding fragments of antibodies, i.e. antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, e.g. fragments that retain one or more CDR regions. Examples of antibody binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, e.g., sc-Fv; nanobodies and multispecific antibodies formed from antibody fragments.

[0089] A “Fab fragment” is comprised of one light chain and the C_{H1} and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule.

[0090] An “Fc” region contains two heavy chain fragments comprising the C_{H1} and C_{H2} domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_{H3} domains.

[0091] In some embodiments, the antibodies, or antigen fragments herein, comprise a Fc region. In some embodiments, the Fc region comprises a mutation that extends the half-life of the antibody when linked to the Fc region. In some embodiments, the Fc region comprises a S228P, L235E, M252Y, S254T, T256E, M428L, N434S, L234F, P331S mutation, or any combination thereof. In some embodiments, the Fc region comprises a M252Y, S254T, and T256E mutations. In some embodiments, the Fc region comprises a S228P and a L235E mutation. In some embodiments, the antibody comprises a L234F, L235E, and P331S mutation. In some embodiments, the Fc region comprises M252Y, S254T, T256E, S228P and L235E mutations. In some embodiments, the Fc region comprises S228P, L235E, M428L, and N434S mutations. In some embodiments, the Fc region comprises the M428L and N434S mutations. In some embodiments, the Fc region comprises the L234F, L235E, P331S, M252Y, S254T, and T256E mutations. Mutations in the Fc region are also described in

US2007041972A1, EP2235059B1, U.S. Patent No. 8,394,925, and Mueller et al, Mol Immunol 1997 Apr;34(6):441-52, each of which is incorporated by reference in its entirety. The numbering referenced herein refers to the Kabat numbering system for the Fc region.

[0092] A “Fab' fragment” contains one light chain and a portion or fragment of one heavy chain that contains the V_H domain and the C_{H1} domain and also the region between the C_{H1} and C_{H2} domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form a F(ab')₂ molecule.

[0093] A “F(ab')₂ fragment” contains two light chains and two heavy chains containing a portion of the constant region between the C_{H1} and C_{H2} domains, such that an interchain disulfide bond is formed between the two heavy chains. A F(ab')₂ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

[0094] The “Fv region” comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

[0095] The term “single-chain Fv” or “scFv” antibody refers to antibody fragments comprising the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv, see Pluckthun (1994) THE PHARMACOLOGY OF MONOCLONAL ANTIBODIES, vol. 113, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315. See also, International Patent Application Publication No. WO 88/01649 and U.S. Pat. Nos. 4,946, 778 and 5,260,203.

[0096] A “domain antibody” is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody may target the same or different antigens.

[0097] A “bivalent antibody” comprises two antigen binding sites. In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific (see below).

[0098] In certain embodiments, monoclonal antibodies herein also include camelized single domain antibodies. See, e.g., Muyldermans *et al.* (2001) *Trends Biochem. Sci.* 26:230; Reichmann *et al.* (1999) *J. Immunol. Methods* 231:25; WO 94/04678; WO 94/25591; U.S. Pat.

No. 6,005,079). In one embodiment, the present invention provides single domain antibodies comprising two V_H domains with modifications such that single domain antibodies are formed.

[0099] As used herein, the term “diabodies” refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H - V_L or V_L - V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, EP 404,097; WO 93/11161; and Holliger *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90: 6444-6448. For a review of engineered antibody variants generally see Holliger and Hudson (2005) *Nat. Biotechnol.* 23:1126-1136.

[00100] Typically, a variant antibody or antigen binding fragment of the antibodies provided herein retain at least 10% of its IGF-1R binding activity (when compared to a parental antibody that is modified) when that activity is expressed on a molar basis. In some embodiments, a variant antibody (or antigen fragment thereof), or antigen binding fragment of an antibody provided herein, retains at least 20%, 50%, 70%, 80%, 90%, 95% or 100% or more of the IGF-1R binding affinity as the parental antibody. As described herein, it is also intended that an antibody or antigen binding fragment of the invention can include conservative or non-conservative amino acid substitutions, which can also be referred to as “conservative variants” or “function conserved variants” of the antibody, that do not substantially alter its biologic activity.

[00101] “Isolated antibody” refers to the purification status of a binding compound and in such context means the molecule is substantially free of other biological molecules such as nucleic acids, proteins, lipids, carbohydrates, or other material such as cellular debris and growth media. Generally, the term “isolated” is not intended to refer to a complete absence of such material or to an absence of water, buffers, or salts, unless they are present in amounts that substantially interfere with experimental or therapeutic use of the binding compound as described herein.

[00102] The term “monoclonal antibody”, as used herein, refers to population of substantially homogeneous antibodies, *i.e.*, the antibody molecules comprising the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in

their variable domains, particularly their CDRs, that are often specific for different epitopes. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.* (1975) *Nature* 256: 495, or may be made by recombinant DNA methods (*see, e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.* (1991) *Nature* 352: 624-628 and Marks *et al.* (1991) *J. Mol. Biol.* 222: 581-597, for example. *See also* Presta (2005) *J. Allergy Clin. Immunol.* 116:731.

[00103] As used herein, a “chimeric antibody” is an antibody having the variable domain from a first antibody and constant domain from a second antibody, where the first and second antibodies are from different species. (U.S. Pat. No. 4,816,567; and Morrison *et al.*, (1984) *Proc. Natl. Acad. Sci. USA* 81: 6851-6855). Typically, the variable domains are obtained from an antibody from an experimental animal (the “parental antibody”), such as a rodent, and the constant domain sequences are obtained from human antibodies, so that the resulting chimeric antibody will be less likely to elicit an adverse immune response in a human subject than the parental (e.g. rodent) antibody.

[00104] As used herein, the term “humanized antibody” refers to forms of antibodies that contain sequences from both human and non-human (*e.g.*, murine, rat) antibodies. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin, and all or substantially all of the framework (FR) regions are those of a human immunoglobulin sequence. The humanized antibody may optionally comprise at least a portion of a human immunoglobulin constant region (Fc).

[00105] The term “fully human antibody” refers to an antibody that comprises human immunoglobulin protein sequences only. A fully human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” refers to an antibody that comprises mouse immunoglobulin sequences only. Alternatively, a fully human antibody may contain rat carbohydrate chains if produced in a rat, in a rat cell, or in a hybridoma derived from a rat cell. Similarly, “rat antibody” refers to an antibody that comprises rat immunoglobulin sequences only.

[00106] In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one “light” (about 25 kDa) and one “heavy” chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the variable and constant regions are joined by a “J” region of about 12 or more amino acids, with the heavy chain also including a “D” region of about 10 more amino acids. See generally, Fundamental Immunology Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989).

[00107] The variable regions of each light/heavy chain pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

[00108] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called complementarity determining regions (CDRs), located within relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chains variable domains comprise FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, Kabat, *et al.*; National Institutes of Health, Bethesda, Md. ; 5th ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32:1-75; Kabat, *et al.*, (1977) J. Biol. Chem. 252:6609-6616; Chothia, *et al.*, (1987) J Mol. Biol. 196:901-917 or Chothia, *et al.*, (1989) Nature 342:878-883.

[00109] As used herein, the term “hypervariable region” refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a “complementarity determining region” or “CDR” (*i.e.* residues 24-34 (CDRL1), 50-56 (CDRL2) and 89-97 (CDRL3) in the light chain variable domain and residues 31-35 (CDRH1), 50-65 (CDRH2) and 95-102 (CDRH3) in the heavy chain variable domain; Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.) and/or those residues from a “hypervariable loop” (*i.e.* residues 26-32 (CDRL1), 50-52 (CDRL2) and 91-96

(CDRL3) in the light chain variable domain and 26-32 (CDRH1), 53-55 (CDRH2) and 96-101 (CDRH3) in the heavy chain variable domain; Chothia and Lesk (1987) *J. Mol. Biol.* 196: 901-917). As used herein, the term “framework” or “FR” residues refers to those variable domain residues other than the hypervariable region residues defined herein as CDR residues. CDRs provide the majority of contact residues for the binding of the antibody to the antigen or epitope. CDRs of interest can be derived from donor antibody variable heavy and light chain sequences, and include analogs of the naturally occurring CDRs, which analogs also share or retain the same antigen binding specificity and/or neutralizing ability as the donor antibody from which they were derived.

[00110] Additionally, in some embodiments, the antibodies can take the form of a full length antibody, single-domain antibody, a recombinant heavy-chain-only antibody (VHH), a single-chain antibody (scFv), a shark heavy-chain-only antibody (VNAR), a microprotein (cysteine knot protein, knottin), a DARPin; a Tetranectin; an Affibody; a Transbody; an Anticalin; an AdNectin; an Affilin; a Microbody; a peptide aptamer; an alterase; a plastic antibody; a phylomer; a stradobody; a maxibody; an evibody; a fynomer, an armadillo repeat protein, a Kunitz domain, an avimer, an atrimer, a probody, an immunobody, a triomab, a troybody; a pepbody; a vaccibody, a UniBody; Affimers, a DuoBody, a Fv, a Fab, a Fab', a F(ab')₂, a peptide mimetic molecule, or a synthetic molecule, as described in US Patent Nos. or Patent Publication Nos. US 7,417,130, US 2004/132094, US 5,831,012, US 2004/023334, US 7,250,297, US 6,818,418, US 2004/209243, US 7,838,629, US 7,186,524, US 6,004,746, US 5,475,096, US 2004/146938, US 2004/157209, US 6,994,982, US 6,794,144, US 2010/239633, US 7,803,907, US 2010/119446, and/or US 7,166,697, the contents of each of which are hereby incorporated by reference in their entireties. See also, Storz MABs. 2011 May-Jun; 3(3): 310-317, which is hereby incorporated by reference.

[00111] The term “antigen” as used herein means any molecule that has the ability to generate antibodies either directly or indirectly or that binds to antibody. Included within the definition of “antigen” is a protein-encoding nucleic acid. An “antigen” can also refer to the binding partner of an antibody. In some embodiments, the antigen is the IGF-1R protein expressed on the surface of a cell. In some embodiments, the cell is an intact cell. An intact cell is a cell that has not been lysed or broken open with the use of detergents or other reagents. A cell that has been treated with detergents or other reagents that breaks up the cellular membrane or punches holes in a cellular membrane is not an intact cell. For example, methods

are provided herein for generating an antibody that binds to an IGF-1R protein, the method comprising culturing a cell comprising a nucleic acid molecule encoding the IGF-1R antibody.

[00112] As used herein, “specific binding” or “immunospecific binding” or “binds immunospecifically” refer to antibody binding to a predetermined antigen (*e.g.* IGF-1R) or epitope present on the antigen. In some embodiments, the antibody binds with a dissociation constant (K_D) of 10^{-7} M or less, and binds to the predetermined antigen with a K_D that is at least two-fold less than its K_D for binding to a non-specific antigen (*e.g.*, BSA, casein, or another non-specific polypeptide) other than the predetermined antigen. The phrases “an antibody recognizing IGF-1R” “an antibody specific for IGF-1R” are used interchangeably herein with the term “an antibody which binds immunospecifically to IGF-1R.” Reference in the present disclosure may be made to IGF-1R. The degree of specificity necessary for an anti-IGF-1R antibody may depend on the intended use of the antibody, and at any rate is defined by its suitability for use for an intended purpose. In some embodiments, the antibody, or binding compound derived from the antigen-binding site of an antibody, of the contemplated method binds to its antigen (IGF-1R), with an affinity that is at least two fold greater, at least ten times greater, at least 20-times greater, or at least 100-times greater than the affinity with any other antigen.

[00113] Methods for determining mAb specificity and affinity by competitive inhibition can be found in Harlow, et al., *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988), Colligan et al., eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, N.Y., (1992, 1993), and Muller, *Meth. Enzymol.* 92:589 601 (1983), which references are entirely incorporated herein by reference.

[00114] The term “homolog” means protein sequences having between 40% and 100% sequence homology or identity to a reference sequence. Percent identity between two peptide chains can be determined by pair wise alignment using the default settings of the AlignX module of Vector NTI v.9.0.0 (Invitrogen Corp., Carlsbad, Calif.). In some embodiments, the antibody, or antigenic binding fragment thereof has, at least 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% homology or identity to a sequence described herein. In some embodiments, the antibody has conservative substitutions as compared to a sequence described herein. Exemplary conservative substitutions are illustrated in **Table 1** and are encompassed within the scope of the disclosed subject matter. The conservative substitution may reside in the framework regions, or in antigen-binding sites, as long they do not adversely affect the

properties of the antibody. Substitutions may be made to improve antibody properties, for example stability or affinity. Conservative substitutions will produce molecules having functional and chemical characteristics similar to those molecules into which such modifications are made. Exemplary amino acid substitutions are shown in **Table 1** below.

Table 1: Exemplary Conservative Substitutions:	
Original Residue	Exemplary Conservative Substitutions
Ala	Val, Leu, Ile
Arg	Lys, Gln, Asn
Asn	Gln
Asp	Glu
Cys	Ser, Ala
Gln	Asn
Gly	Pro, Ala
His	Asn, Gln, Lys, Arg
Ile	Leu, Val, Met, Ala, Phe
Leu	Ile, Val, Met, Ala, Phe
Lys	Arg, Gln, Asn
Met	Leu, Phe, Ile
Phe	Leu, Val, Ile, Ala, Tyr
Pro	Ala
Ser	Thr, Ala, Cys
Thr	Ser
Trp	Tyr, Phe
Tyr	Trp, Phe, Thr, Ser
Val	Ile, Met, Leu, Phe, Ala

[00115] In some embodiments, variants of the proteins and peptides provided herein are provided. In some embodiments, a variant comprises a substitution, deletions, or insertion. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) substitutions. As described herein, the substitutions can be conservative substitutions. In some embodiments, the substitution is non-conservative. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) deletions. In some embodiments, the variant comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (*e.g.*, 1-10) insertions. In some embodiments, the substitutions, deletions, or insertions are present in the CDRs provided for herein. In some embodiments, the substitutions, deletions, or insertions are not present in the CDRs provided for herein.

[00116] The term “in combination with” as used herein means that the described agents can be administered to an animal or subject together in a mixture, concurrently as single agents or sequentially as single agents in any order.

[00117] The techniques to raise antibodies to small peptide sequences that recognize and bind to those sequences in the free or conjugated form or when presented as a native sequence

in the context of a large protein are well known in the art. Such antibodies include murine, murine-human and human-human antibodies produced by hybridoma or recombinant techniques known in the art. Antibodies can also be produced in human, a mouse, sheep, a rat, a rabbit, a shark, a llama, or a chicken. In some embodiments, the antibody is produced in a chicken. The antibodies can also be produced in or other small animals.

[00118] The term “epitope” is meant to refer to that portion of any molecule capable of being recognized by and bound by an antibody at one or more of the Ab’s antigen binding regions. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and have specific three-dimensional structural characteristics as well as specific charge characteristics. Example of epitopes include, but are not limited to, the residues described herein that form IGF-1R epitopes. In some embodiments, the epitope is only present in a non-denatured protein. In some embodiments, the epitope is only present in a denatured protein.

[00119] In some embodiments, the source for the DNA encoding a non-human antibody include cell lines which produce antibody, such as hybrid cell lines commonly known as hybridomas.

[00120] The hybrid cells are formed by the fusion of a non-human antibody-producing cell, typically a spleen cell of an animal immunized against either natural or recombinant antigen, or a peptide fragment of the antigen protein sequence. Alternatively, the non-human antibody-producing cell can be a B lymphocyte obtained from the blood, spleen, lymph nodes or other tissue of an animal immunized with the antigen.

[00121] The second fusion partner, which provides the immortalizing function, can be a lymphoblastoid cell or a plasmacytoma or myeloma cell, which is not itself an antibody producing cell, but is malignant. Fusion partner cells include, but are not limited to, the hybridoma SP2/0-Ag14, abbreviated as SP2/0 (ATCC CRL1581) and the myeloma P3X63Ag8 (ATCC TIB9), or its derivatives. See, e.g. Ausubel *infra*, Harlow *infra*, and Colligan *infra*, the contents of which references are incorporated entirely herein by reference.

[00122] The antibodies can be generated according to the examples provided herein and other methods known in the art, such as disclosed in U.S. Patent No. 11,548,951, which is hereby incorporated by reference in its entirety. Once the sequences are known, the antibodies can also be generated according to known methods. The antibodies can also be converted to different types, such as being converted to Human IgGs and the like. By converting the antibodies to a human antibody, a human subject should not identify the antibodies as foreign.

The conversion of a non-human IgG antibody to a human IgG antibody is well known and can routinely be done once the native sequence is known. As discussed herein, the antibodies can be modified according to known methods. Such methods are described in, for example, Riechmann L, Clark M, Waldmann H, Winter G (1988). Reshaping human antibodies for therapy". Nature 332 (6162): 332–323; Tsurushita N, Park M, Pakabunto K, Ong K, Avdalovic A, Fu H, Jia A, Vásquez M, Kumar S. (2004). The antibody-producing cell contributing the nucleotide sequences encoding the antigen-binding region of the chimeric antibody can also be produced by transformation of a non-human, such as a primate, or a human cell. For example, a B lymphocyte which produces the antibody can be infected and transformed with a virus such as Epstein-Barr virus to yield an immortal antibody producing cell (Kozbor et al., Immunol. Today 4:72 79 (1983)). Alternatively, the B lymphocyte can be transformed by providing a transforming gene or transforming gene product, as is well-known in the art. See, e.g., Ausubel *infra*, Harlow *infra*, and Colligan *infra*, the contents of which references are incorporated entirely herein by reference. The cell fusions are accomplished by standard procedures well known to those skilled in the field of immunology. Fusion partner cell lines and methods for fusing and selecting hybridomas and screening for mAbs are well known in the art. See, e.g., Ausubel *infra*, Harlow *infra*, and Colligan *infra*, the contents of which references are incorporated entirely herein by reference.

Antibodies

[00123] In some embodiments, the antibody is a MAb which binds to IGF-1R. In some embodiments, the antibody binds to amino acids of an epitope of the IGF-1R.

[00124] In some embodiments, the antibody comprises a sequence as provided for herein.

[00125] The sequences of the antibodies can be modified to yield human IgG antibodies. The conversion of the sequences provided herein can be modified to yield other types of antibodies. The CDRs can also be linked to other antibodies, proteins, or molecules to create antibody fragments that bind to IGF-1R. This can be in the form of an antibody drug conjugate ("ADC"), a multi-specific molecule, or a chimeric antigen receptor. The CDRs and antibody sequences provided herein also be humanized or made fully human according to known methods. The sequences can also be made into chimeric antibodies as described herein.

[00126] In some embodiments, the antibody comprises an amino acid sequence comprising a sequence provided for herein or a fragment thereof. In some embodiments, the antibody comprises one or more amino acid sequences as provided herein, an antigen binding

fragments, thereof, or a human IgG variant thereof. “A human IgG variant thereof” refers to an antibody that has been modified to be a human IgG when the starting antibody is not a human IgG antibody.

[00127] As described herein the production of antibodies with a known sequence is routine and can be done by any method. Accordingly, in some embodiments, a nucleic acid encoding an antibody or fragment thereof is provided. In some embodiments, the nucleic acid encodes a sequence provided for herein. The antibodies can also be modified to be chimeric antibodies or human antibodies. The antibodies can also be used in injectable pharmaceutical compositions. As also described herein, the antibodies can be isolated antibodies or engineered antibodies.

[00128] In some embodiments, “derivatives” of the antibodies, fragments, regions or derivatives thereof, which term includes those proteins encoded by truncated or modified genes to yield molecular species functionally resembling the immunoglobulin fragments are provided. The modifications include, but are not limited to, addition of genetic sequences coding for cytotoxic proteins such as plant and bacterial toxins. The modification can also include a reporter protein, such as a fluorescent or chemiluminescent tag. The fragments and derivatives can be produced in any manner.

[00129] The identification of these antigen binding region and/or epitopes recognized by Abs described herein provide the information necessary to generate additional monoclonal antibodies with similar binding characteristics and therapeutic or diagnostic utility that parallel the embodiments of this application.

[00130] The nucleic acid sequence encoding an antibody described herein can be genomic DNA or cDNA, or RNA (*e.g.* mRNA) which encodes at least one of the variable regions described herein. A convenient alternative to the use of chromosomal gene fragments as the source of DNA encoding the V region antigen-binding segment is the use of cDNA for the construction of chimeric immunoglobulin genes, *e.g.*, as reported by Liu et al. (Proc. Natl. Acad. Sci., USA 84:3439 (1987) and J. Immunology 139:3521 (1987), which references are hereby entirely incorporated herein by reference. The use of cDNA requires that gene expression elements appropriate for the host cell be combined with the gene in order to achieve synthesis of the desired protein. The use of cDNA sequences is advantageous over genomic sequences (which contain introns), in that cDNA sequences can be expressed in bacteria or other hosts which lack appropriate RNA splicing systems.

[00131] For example, a cDNA encoding a V region antigen-binding segment able to detect, bind to, or neutralize an IGF-1R antigen can be provided using known methods based on the use of the amino acid sequences provided herein. Because the genetic code is degenerate, more than one codon can be used to encode a particular amino acid (Watson, et al., *infra*). Using the genetic code, one or more different oligonucleotides can be identified, each of which would be capable of encoding the amino acid. The probability that a particular oligonucleotide will, in fact, constitute the actual XXX-encoding sequence can be estimated by considering abnormal base pairing relationships and the frequency with which a particular codon is actually used (to encode a particular amino acid) in eukaryotic or prokaryotic cells expressing an antibody or fragment. Such “codon usage rules” are disclosed by Lathe, et al., *J. Molec. Biol.* 183:1 12 (1985). Using the “codon usage rules” of Lathe, a single oligonucleotide, or a set of oligonucleotides, that contains a theoretical “most probable” nucleotide sequence capable of encoding an antibody variable or constant region sequences is identified.

[00132] The variable regions described herein can be combined with any type of constant region including a human constant region or murine constant region. Human genes which encode the constant (C) regions of the antibodies, fragments and regions can be derived from a human fetal liver library, by known methods. Human C regions genes can be derived from any human cell including those which express and produce human immunoglobulins. The human C_H region can be derived from any of the known classes or isotypes of human H chains, including gamma, μ , α , δ or ϵ , and subtypes thereof, such as G1, G2, G3 and G4. Since the H chain isotype is responsible for the various effector functions of an antibody, the choice of C_H region will be guided by the desired effector functions, such as complement fixation, or activity in antibody-dependent cellular cytotoxicity (ADCC). Preferably, the C_H region is derived from gamma 1 (IgG1), gamma 3 (IgG3), gamma 4 (IgG4), or μ (IgM). The human C_L region can be derived from either human L chain isotype, kappa or lambda. In some embodiments, the antibody comprises a Fc domain. In some embodiments, the Fc domain comprises a mutation to extend the half-life of the antibody. In some embodiments, the Fc domain comprises a mutation such as those described in U.S. Patent No. 7,670,600, which is hereby incorporated by reference in its entirety. In some embodiment, the constant region comprises a mutation at position at amino acid residue 428 relative to a wild-type human IgG constant domain, numbered according to the EU numbering index of Kabat. Without being bound to any particular theory, an antibody comprising a mutation that corresponds to residue 428 can have

an increased half-life compared to the half-life of an IgG having the wild-type human IgG constant domain. In some embodiments, the mutation is a substitution of the native residue with a threonine, leucine, phenylalanine or serine. In some embodiments, the antibody further comprises one or more amino acid substitutions relative to the corresponding wild-type human IgG constant domain at one or more of amino acid residues 251-256, 285-290, 308-314, 385-389, and 429-436, numbered according to the Kabat EU numbering index. The specific mutations or substitutions at these positions are described in U.S. Patent No. 7,670,600, which is hereby incorporated by reference in its entirety.

[00133] Genes encoding human immunoglobulin C regions can be obtained from human cells by standard cloning techniques (Sambrook, et al. (Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (1989) and Ausubel et al., eds. Current Protocols in Molecular Biology (1987 1993)). Human C region genes are readily available from known clones containing genes representing the two classes of L chains, the five classes of H chains and subclasses thereof. Chimeric antibody fragments, such as F(ab')₂ and Fab, can be prepared by designing a chimeric H chain gene which is appropriately truncated. For example, a chimeric gene encoding an H chain portion of an F(ab')₂ fragment would include DNA sequences encoding the CH₁ domain and hinge region of the H chain, followed by a translational stop codon to yield the truncated molecule.

[00134] In some embodiments, the antibodies, murine, human, humanized, or chimeric antibodies, fragments and regions of the antibodies described herein are produced by cloning DNA segments encoding the H and L chain antigen-binding regions of an IGF-1R antigen specific antibody, and joining these DNA segments to DNA segments encoding C_H and C_L regions, respectively, to produce murine, human or chimeric immunoglobulin-encoding genes.

[00135] Thus, in some embodiments, a fused chimeric gene is created which comprises a first DNA segment that encodes at least the antigen-binding region of non-human origin, such as a functionally rearranged V region with joining (J) segment, linked to a second DNA segment encoding at least a part of a human C region.

[00136] Therefore, cDNA encoding the antibody V and C regions, the method of producing the antibody according to some of the embodiments described herein involve several steps, as exemplified below: 1. isolation of messenger RNA (mRNA) from the cell line producing an anti- IGF-1R antigen antibody and from optional additional antibodies supplying heavy and light constant regions; cloning and cDNA production therefrom; 2. preparation of a full length cDNA library from purified mRNA from which the appropriate V and/or C region

gene segments of the L and H chain genes can be: (i) identified with appropriate probes, (ii) sequenced, and (iii) made compatible with a C or V gene segment from another antibody for a chimeric antibody; 3. Construction of complete H or L chain coding sequences by linkage of the cloned specific V region gene segments to cloned C region gene, as described above; 4. Expression and production of L and H chains in selected hosts, including prokaryotic and eukaryotic cells to provide murine-murine, human-murine, human-human or human murine antibodies.

[00137] Two coding DNA sequences are said to be “operably linked” if the linkage results in a continuously translatable sequence without alteration or interruption of the triplet reading frame. A DNA coding sequence is operably linked to a gene expression element if the linkage results in the proper function of that gene expression element to result in expression of the coding sequence.

[00138] As used herein and unless otherwise indicated, the term “about” is intended to mean $\pm 5\%$ of the value it modifies. Thus, about 100 means 95 to 105.

[00139] In some embodiments, the antibodies described herein are used to detect the presence of the antigen. The present antibody can be used in any device or method to detect the presence of the antigen.

[00140] The term “purified” with referenced to an antibody refers to an antibody that is substantially free of other material that associates with the molecule in its natural environment. For instance, a purified protein is substantially free of the cellular material or other proteins from the cell or tissue from which it is derived. The term refers to preparations where the isolated protein is sufficiently pure to be analyzed, or at least 70% to 80% (w/w) pure, at least 80%-90% (w/w) pure, 90-95% pure; and at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure. In some embodiments, the antibody is purified.

[00141] As an alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide may be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with a polypeptide described herein to thereby isolate immunoglobulin library members that bind to the polypeptide. Techniques and commercially available kits for generating and screening phage display libraries are well known to those skilled in the art. Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody or antigen binding protein display libraries can be found in the literature. Thus, the

epitopes described herein can be used to screen for other antibodies that can be used therapeutically, diagnostically, or as research tools.

Antibody Conjugates

[00142] The antibodies provided for herein may also be conjugated to a chemical moiety. The chemical moiety may be, *inter alia*, a polymer, a radionuclide or a cytotoxic factor. In some embodiments, this can be referred to as an antibody drug conjugate. In some embodiments, the chemical moiety is a polymer which increases the half-life of the antibody molecule in the body of a subject. Suitable polymers include, but are not limited to, polyethylene glycol (PEG) (*e.g.*, PEG with a molecular weight of 2kDa, 5 kDa, 10 kDa, 12kDa, 20 kDa, 30kDa or 40kDa), dextran and monomethoxypolyethylene glycol (mPEG). Lee, *et al.*, (1999) (Bioconj. Chem. 10:973-981) discloses PEG conjugated single-chain antibodies. Wen, *et al.*, (2001) (Bioconj. Chem. 12:545-553) disclose conjugating antibodies with PEG which is attached to a radiometal chelator (diethylenetriaminopentaacetic acid (DTPA)). Examples of chemical moieties include, but are not limited to, anti-mitotics, such as calicheamicins (*e.g.* ozogamicin), monomethyl auristatin E, mertansine, and the like. Other examples include, but are not limited to, biologically active anti-microtubule agents, alkylating agents and DNA minor groove binding agents. Other examples of are provided herein and below. The chemical moiety can be linked to the antibody through a linking group (maleimide), a cleavable linker, such as a cathepsin cleavable linkers (valine-citrulline), and in some embodiments, one or more spacers (*e.g.* para-aminobenzylcarbamate). Without being bound to any particular theory, once the antibody conjugate binds IGF-1R it can be internalized and the chemical moiety can kill the cell or otherwise inhibit its growth. In some embodiments, the cell is a thyroid cell.

[00143] The antibodies and antibody fragments of the invention may also be conjugated with labels such as ⁹⁹Tc, ⁹⁰Y, ¹¹¹In, ³²P, ¹⁴C, ¹²⁵I, ³H, ¹³¹I, ¹¹C, ¹⁵O, ¹³N, ¹⁸F, ³⁵S, ⁵¹Cr, ⁵⁷To, ²²⁶Ra, ⁶⁰Co, ⁵⁹Fe, ⁵⁷Se, ¹⁵²Eu, ⁶⁷CU, ²¹⁷Ci, ²¹¹At, ²¹²Pb, ⁴⁷Sc, ¹⁰⁹Pd, ²³⁴Th, and ⁴⁰K, ¹⁵⁷Gd, ⁵⁵Mn, ⁵²Tr and ⁵⁶Fe.

[00144] The antibodies and antibody fragments may also be conjugated with fluorescent or chemiluminescent labels, including fluorophores such as rare earth chelates, fluorescein and its derivatives, rhodamine and its derivatives, isothiocyanate, phycoerythrin, phycocyanin, allophycocyanin, o-phthalaldehyde, fluorescamine, ¹⁵²Eu, dansyl, umbelliferone, luciferin, luminal label, isoluminal label, an aromatic acridinium ester label, an imidazole label, an

acridinium salt label, an oxalate ester label, an aequorin label, 2,3-dihydrophthalazinediones, biotin/avidin, spin labels and stable free radicals.

[00145] The antibody molecules may also be conjugated to a cytotoxic factor such as diphtheria toxin, *Pseudomonas aeruginosa* exotoxin A chain, ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins and compounds (*e.g.*, fatty acids), dianthin proteins, *Phytolacca americana* proteins PAPI, PAPII, and PAP-S, *momordica charantia* inhibitor, curcumin, croton, *saponaria officinalis* inhibitor, mitogellin, restrictocin, phenomycin, and enomycin.

[00146] Any method known in the art for conjugating the antibody molecules of the invention to the various moieties may be employed, including those methods described by Hunter, *et al.*, (1962) *Nature* 144:945; David, *et al.*, (1974) *Biochemistry* 13:1014; Pain, *et al.*, (1981) *J. Immunol. Meth.* 40:219; and Nygren, J., (1982) *Histochem. and Cytochem.* 30:407. Methods for conjugating antibodies are conventional and very well known in the art.

Chimeric Antigen Receptors

[00147] The antibodies provided herein can also be incorporated into a chimeric antigen receptor (“CAR”) that can be used, for example, in a CAR-T cell. In some embodiments, the extracellular domain of the CAR can be an antibody as provided for herein. In some embodiments, the antibody is in a scFv format. CAR-T cells are a type of treatment in which a patient’s T cells are modified so they will attack the cells that are expressing IGF-1R. T cells are taken from a patient’s blood. Then the gene for a special receptor that binds to a certain protein on the patient’s cells is added in the laboratory. In some embodiments, the receptor binds to IGF-1R using the binding regions of the antibodies provided for herein. The CAR-T cells comprising the IGF-1R antibody can then be used to treat a condition, such as those provided for herein.

Insulin-like Growth Factor 1 Receptor (IGF-1R) Antibodies

[00148] In some embodiments, antibodies (*e.g.* an anti-IGF-1R antibody) are provided herein. In some embodiments, the antibody is a recombinant antibody that binds to an IGF-1R protein. In some embodiments, the IGF-1R protein is a human IGF-1R protein. In some embodiments, the IGF-1R protein that is recognized by the antibodies is in its native conformation (non-denatured) conformation. In some embodiments, the antibody does not specifically bind to a denatured IGF-1R protein. As used herein, the term “recombinant antibody” refers to an antibody that is not naturally occurring. In some embodiments, the term “recombinant antibody” refers to an antibody that is not isolated from a human subject.

[00149] In some embodiments, the antibody comprises one or more peptides having the following sequences, or a variant thereof:

Antibody	LCDR1 Sequence	LCDR2 Sequence	LCDR3 Sequence	HCDR1 Sequence	HCDR2 Sequence	HCDR3 Sequence
VRDN-001/VRDN-003	RSSQSI VHSNV NTYLE (SEQ ID NO: 1)	KVSNRF S (SEQ ID NO: 2)	FQGSHV PPT (SEQ ID NO: 3)	SYWMH (SEQ ID NO: 4)	GEINPSNG RTNYNQKF QG (SEQ ID NO: 5)	GRPDYY GSSKWW FDV (SEQ ID NO: 6)
VRDN-002	RSSQSI VHSNG NTYLQ WYLQ (SEQ ID NO: 12)	KVSNRL Y (SEQ ID NO: 13)	FQGSHV PWT (SEQ ID NO: 14)	GGYLWN (SEQ ID NO: 15)	YISYDGTN NYKPSLKD (SEQ ID NO: 16)	YGRVFFD Y (SEQ ID NO: 17)
Teprotumumab	RASQSV SSYLA (SEQ ID NO: 22)	DASKRA T (SEQ ID NO: 23)	QQRSKW PPWT (SEQ ID NO: 24)	SYGMH (SEQ ID NO: 25)	IIWFDGSST YYADSVR G (SEQ ID NO: 26)	ELGRRYF DL (SEQ ID NO: 27)

Antibody	Light Chain Variable Region (VL) Sequence	Heavy Chain Variable Region (VH) Sequence	Light Chain (LC) Sequence	Heavy Chain (HC) Sequence
VRDN-001	DVVMQT TPLSLPV SLGDPAS ISCRSSQ SIVHSNV NTYLEW YLQKPG QSPRLLI YKVSNR FSGVPD RFSGSG AGTDFT LRISRVE AEDLGIY YCFQGS HVPPTFG GGTKLEI K (SEQ ID NO: 7)	QVQLVQSGAE VVKPGASVKL SCKASGYTFTS YWMHWVKQR PGQGLEWIGE NPSNGRTNYN QKFQGKATLT VDKSSSTAYM QLSSLTSEDSA VYYFARGRPD YYGSSKWFYD VWGQGTTVT VSS (SEQ ID NO: 8)	DVVMQTQPLS LPVSLGDPASI SCRSSQSIVHS NVNTYLEWYL QKPGQSPRLLI YKVSNRFSGV PDRFSGSGAG TDFTLRISRVE AEDLGIYYCF QGSHVPPTFG GGTKLEIKRTV AAPSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSSTLT SKADYEKHKV YACEVTHQGL SSPVTKSFNRG EC (SEQ ID NO: 9)	QVQLVQSGAE VVKPGASVKL SCKASGYTFTS YWMHWVKQR PGQGLEWIGE NPSNGRTNYN QKFQGKATLT VDKSSSTAYM QLSSLTSEDSA VYYFARGRPD YYGSSKWFYD VWGQGTTVT VSSASTKGPSV FPLAPSSKSTS GGTAALGCLV KDYPFEPVTVS WNSGALTSGV HTFPAVLQSSG LYSLSSVTVTP SSSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSVF

Antibody	Light Chain Variable Region (VL) Sequence	Heavy Chain Variable Region (VH) Sequence	Light Chain (LC) Sequence	Heavy Chain (HC) Sequence
				LFPPKPKDTL MISRTPEVTCV VVDVSHEDPE VKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYK CKVSNKALPA PIEKTISKAKG QPREPQVYTLF PSRDELTKNQ VSLTCLVKGF YPSDIAVEWES NGQPENNYKT TPPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLSP GK (SEQ ID NO: 10)
VRDN-003	DVVMQT TPLSLPV SLGDPAS ISCRSSQ SIVHSNV NTYLEW YLQKPG QSPRLLI YKVSNR FSGVPD RFGSG AGTDFT LRISRVE AEDLGIY YCFQGS HVPPTFG GGTKLEI K (SEQ ID NO: 7)	QVQLVQSGAE VVKPGASVKL SCKASGYTFTS YWMHWVKQR PGQGLEWIGEI NPSNGRTNYN QKFQGKATLT VDKSSSTAYM QLSSLTSEDSA VYYFARGRPD YYGSSKWFYD VWGQGTTVT VSS (SEQ ID NO: 8)	DVVMQTPLS LPVSLGDPASI SCRSSQSIVHS NVNTYLEWYL QKPGQSPRLLI YKVSNRFSGV PDRFSGSGAG TDFTLRISRVE AEDLGIYCF QGSHVPPTFG GGTKLEIKRTV AAPSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSITLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNRG EC (SEQ ID No: 9)	QVQLVQSGAE VVKPGASVKL SCKASGYTFTS YWMHWVKQR PGQGLEWIGEI NPSNGRTNYN QKFQGKATLT VDKSSSTAYM QLSSLTSEDSA VYYFARGRPD YYGSSKWFYD VWGQGTTVT VSSASTKGPSV FPLAPSSKSTS GGTAALGCLV KDYFPEPVTVS WNSGALTSGV HTFPAVLQSSG LYSLSSVVTVP SSSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSVF

Antibody	Light Chain Variable Region (VL) Sequence	Heavy Chain Variable Region (VH) Sequence	Light Chain (LC) Sequence	Heavy Chain (HC) Sequence
				LFPPKPKDTLY ITREPEVTCVV VDVSHEDPEV KFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNQKEYKC KVSNAKALPAPI EKTISKAKGQP REPQVYTLPPS RDELTKNQVS LTCLVKGFYPS DIAVEWESNG QPENNYKTTT PVLDSGGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNH YTQKSLSLSPG (SEQ ID NO: 11)
VRDN-002	DIVMTQ SPLSLPV TPGEPAS ISCRSSQ SIVHSNG NTYLQW YLQKPG QSPQLLI YKVSNR LYGVDP RFSGSGS GTDFTL KISRVEA EDVGYY YCFQGS HVPWTF GQGTKV EIKR (SEQ ID NO: 18)	QVQLQESGPG LVKPSETLSLT CTVSGYSITGG YLWNWIRQPP GKGLEWIGYIS YDGTNNYKPS LKDRVITSRDT SKNQFSLKLSS VTAADTAVYY CARYGRVFFD YWGGQTLVT VSS (SEQ ID NO: 19)	DIVMTQSPLSL PVTGPGEPAIS CRSSQSIVHSN GNTYLQWYL QKPGQSPQLLI YKVSNRLYGV PDRFSGSGSGT DFTLKISRVEA EDVGYYCFQ GSHVPWTFGQ GTKVEIKRTV AAPSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSITLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNRG EC (SEQ ID NO: 20)	QVQLQESGPG LVKPSETLSLT CTVSGYSITGG YLWNWIRQPP GKGLEWIGYIS YDGTNNYKPS LKDRVITSRDT SKNQFSLKLSS VTAADTAVYY CARYGRVFFD YWGGQTLVT VSSASTKGPSV FPLAPSSKSTS GGTAALGCLV KDYFPEPVTVS WNSGALTSGV HTFPAVLQSSG LYSLSSVITVP SSSLGTQTYIC NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP APPELLGGPSVF LFPPKPKDTLY

Antibody	Light Chain Variable Region (VL) Sequence	Heavy Chain Variable Region (VH) Sequence	Light Chain (LC) Sequence	Heavy Chain (HC) Sequence
				ITREPEVTCVV VDVSHEDPEV KFNWYVDGV EVHNAKTKPR EEQYNSTYRV VSVLTVLHQD WLNQKEYKC KVSNAKALPAPI EKTISKAKGQP REPQVYTLPPS REEMTKNQVS LTCLVKGFYPS DIAVEWESNG QPENNYKTTT PVLDSGGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNH YTQKSLSLSPG (SEQ ID NO: 21)
Teprotumumab	EIVLTQSP ATLSLSP GERATLS CRASQSV SSYLAWY QQKPGQ APRLLIY DASKRAT GIPARFSG SGSGTDF TLTISSLE PEDFAVY YCQQRSK WPPWTF GQGTKVE SK (SEQ ID NO: 28)	QVELVESGGGV VQPGRSQRLSC AASGFTFSSYG MHWVRQAPGK GLEWVAIIWFD GSSTYYADSVR GRFTISRDN SKN TLYLQMNSLRA EDTAVYFCARE LGRRYFDLWGR GTLVSVSS (SEQ ID NO: 29)	EIVLTQSPATL SLSPGERATLS CRASQSVSSYL AWYQQKPGQ APRLLIYDASK RATGIPARFSG SGSGTDFTLTI SSLEPEDFAVY YCQQRSKWPP WTFGQGTKVE SKRTVAAPSV FIFPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLKADYE KHKVYACEVT HQGLSSPVTKS FNRGEC (SEQ ID NO: 30)	QVELVESGGG VVQPGRSQRL SCAASGFTFSS YGMHWVRQA PGKGLEWVAII WFDGSSTYYA DSVRGRFTISR DNSKNTLYLQ MNSLRAEDTA VYFCARELGR RYFDLWGRGT LVSVSSASTKG PSVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLSS VVTVPSSSLGT QTYICNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPELLG GPSVFLFPPKP KDTLMISRTP

Antibody	Light Chain Variable Region (VL) Sequence	Heavy Chain Variable Region (VH) Sequence	Light Chain (LC) Sequence	Heavy Chain (HC) Sequence
				VTCVVVDVSH EDPEVKFNWY VDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNG KEYKCKVSNK ALPAPIEKTISK AKGQPREPQV YTLPPSRDEL T KNQVSLTCLV KGFYPSDIAVE WESNGQPENN YKTPPVLD S DGSFFLYSKLT VDKSRWQQG NVFSCSV MHE ALHNHYTQKS LSLSPGK (SEQ ID NO: 31)

[00150] The VH and the VL sequences can be in any format, including, but not limited to a scFv format where the VH and VL regions are linked with a peptide linker. Examples of peptide linkers that can be used to link various peptides provided for herein include, but are not limited to: (GGGGS)_n (SEQ ID NO: 32); (GGGGA)_n (SEQ ID NO: 33), or any combination thereof, wherein each n is independently 1-5. In some embodiments, the variable regions are not linked with a peptide linker.

[00151] In some embodiments, the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, and a LCDR3 of SEQ ID NO: 3 and the heavy chain comprises a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6. In some embodiments, the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7. In some embodiments, the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence

of SEQ ID NO: 9. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 11. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11. In some embodiments, the antibody comprises a polypeptide that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a polypeptide comprising the sequence of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, or SEQ ID NO: 11, provided that such antibody comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, and a LCDR3 of SEQ ID NO: 3 and the heavy chain comprises a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.

[00152] In some embodiments, the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 12, a LCDR2 of SEQ ID NO: 13, and a LCDR3 of SEQ ID NO: 13 and the heavy chain comprises a HCDR1 of SEQ ID NO: 15, a HCDR2 of SEQ ID NO: 16 and a HCDR3 of SEQ ID NO: 17. In some embodiments, the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19. In some embodiments, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 21. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 21. In some embodiments, the antibody comprises a polypeptide that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a polypeptide comprising the sequence of SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, or SEQ ID NO: 21, provided that such antibody comprises a LCDR1 of SEQ ID NO: 12, a LCDR2 of SEQ ID NO: 13, and a LCDR3 of SEQ ID NO: 13 and the heavy chain comprises a HCDR1 of SEQ ID NO: 15, a HCDR2 of SEQ ID NO: 16 and a HCDR3 of SEQ ID NO: 17.

[00153] In some embodiments, the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 22, a LCDR2 of SEQ ID NO: 23, and a LCDR3 of SEQ ID NO: 24 and the heavy chain comprises a HCDR1 of SEQ ID NO: 25, a HCDR2 of SEQ ID NO: 26 and a HCDR3 of SEQ ID NO: 27. In some embodiments, the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29. In some embodiments, the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 31. In some embodiments, the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 31. In some embodiments, the Fc region of the heavy chain comprises the mutations M252Y, S254T, and T256E, according to EU numbering. In some embodiments, the heavy chain comprises the mutations M428L, and N434S, according to EU numbering. In some embodiments, the antibody comprises a polypeptide that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a polypeptide comprising the sequence of SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31, provided that such antibody comprises a LCDR1 of SEQ ID NO: 22, a LCDR2 of SEQ ID NO: 23, and a LCDR3 of SEQ ID NO: 24 and the heavy chain comprises a HCDR1 of SEQ ID NO: 25, a HCDR2 of SEQ ID NO: 26 and a HCDR3 of SEQ ID NO: 27.

[00154] In some embodiments, the antibody, or antigen binding fragment thereof, comprises a sequence of, or a variant of any of the foregoing.

Pharmaceutical Compositions

[00155] In some embodiments, to prepare pharmaceutical or sterile compositions of the anti-IGF-1R antibodies or other proteins provided herein, the antibody or antigen binding fragment thereof or other proteins provided herein are admixed with a pharmaceutically acceptable carrier or excipient. See, *e.g.*, *Remington's Pharmaceutical Sciences* and *U.S. Pharmacopeia: National Formulary*, Mack Publishing Company, Easton, PA (1984).

[00156] Formulations of therapeutic and diagnostic agents may be prepared by mixing with acceptable carriers, excipients, or stabilizers in the form of, *e.g.*, lyophilized powders,

slurries, aqueous solutions or suspensions (see, *e.g.*, Hardman, *et al.* (2001) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, NY; Gennaro (2000) *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams, and Wilkins, New York, NY; Avis, *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets*, Marcel Dekker, NY; Lieberman, *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Disperse Systems*, Marcel Dekker, NY; Weiner and Kotkoskie (2000) *Excipient Toxicity and Safety*, Marcel Dekker, Inc., New York, NY). In some embodiments, the antibodies are diluted to an appropriate concentration in a sodium acetate solution pH 5-6, and NaCl or sucrose is added for tonicity. Additional agents, such as polysorbate 20 or polysorbate 80, may be added to enhance stability.

[00157] Toxicity and therapeutic efficacy of the antibody compositions, administered alone or in combination with another agent, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index (LD₅₀/ ED₅₀). In particular aspects, antibodies exhibiting high therapeutic indices are desirable. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration.

[00158] In some embodiments, a composition of the invention is administered to a subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)).

[00159] The mode of administration can vary. Suitable routes of administration include oral, rectal, transmucosal, intestinal, parenteral; intramuscular, subcutaneous, intradermal, intramedullary, intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, intraocular, inhalation, insufflation, topical, cutaneous, transdermal, or intra-arterial.

[00160] In some embodiments, the antibody or antigen binding fragment thereof can be administered by an invasive route such as by injection. In some embodiments, the antibodies or antigen binding fragment thereof, or pharmaceutical composition thereof, is administered intravenously, subcutaneously, intramuscularly, intraarterially, intra-articularly (*e.g.* in arthritis

joints), or by inhalation, aerosol delivery. Administration by non-invasive routes (*e.g.*, orally; for example, in a pill, capsule or tablet) is also within the scope of the present embodiments.

[00161] In some embodiments, the anti-IGF-1R antibody, or antigen binding fragment thereof, is administered in combination with at least one additional therapeutic agent, such as, but not limited to any therapeutic used to treat thyroid eye disease. For example, in some embodiments, the anti-IGF-1R antibody, or antigen binding fragment thereof, is administered in combination with at least one additional therapeutic agent, such as, but not limited to a therapeutic used to treat thyroid eye disease or a condition related to the same. Examples of such treatments and therapeutics include, but are not limited to anti-thyroid medications, diabetes medications, beta-blockers, propylthiouracil, methimazole, propranolol, atenolol, metoprolol, nadolol, corticosteroids, metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, regular insulin, insulin aspart, insulin glulisine, insulin lispro, insulin isophane, insulin degludec, insulin detemir, insulin glargine, acerbose, miglitol, acebutolol, atenolol, betaxolol, bisoprolol, cartelol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol, tomlol ophthalmic solution, sitagliptin, saxagliptin, linagliptin, alogliptin, dulaglutide, exenatide, semaglutide, liraglutide, lixisenatide, canagliflozin, dapagliflozin, empagliflozin, or any combination thereof.

[00162] Compositions can be administered with medical devices known in the art. For example, a pharmaceutical composition of the invention can be administered by injection with a hypodermic needle, including, *e.g.*, a prefilled syringe or autoinjector.

[00163] The pharmaceutical compositions may also be administered with a needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556.

[00164] The pharmaceutical compositions may also be administered by infusion. Examples of well-known implants and modules for administering pharmaceutical compositions include: U.S. Patent No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such implants, delivery systems, and modules are well known to those skilled in the art.

[00165] Alternately, one may administer the antibody in a local rather than systemic manner, for example, via injection of the antibody directly into an arthritic joint or pathogen-induced lesion characterized by immunopathology, often in a depot or sustained release formulation. Furthermore, one may administer the antibody in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody, targeting, for example, arthritic joint or pathogen-induced lesion characterized by immunopathology. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

Use of IGF-1R Antibodies

[00166] The administration regimen depends on several factors, including the serum or tissue turnover rate of the therapeutic antibody, the level of symptoms, the immunogenicity of the therapeutic antibody, and the accessibility of the target cells in the biological matrix. Preferably, the administration regimen delivers sufficient therapeutic antibody to effect improvement in the target disease state, while simultaneously minimizing undesired side effects. Accordingly, the amount of biologic delivered depends in part on the particular therapeutic antibody and the severity of the condition being treated. Guidance in selecting appropriate doses of therapeutic antibodies is available (see, *e.g.*, Wawrzynczak (1996) *Antibody Therapy*, Bios Scientific Pub. Ltd, Oxfordshire, UK; Kresina (ed.) (1991) *Monoclonal Antibodies, Cytokines and Arthritis*, Marcel Dekker, New York, NY; Bach (ed.) (1993) *Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases*, Marcel Dekker, New York, NY; Baert, *et al.* (2003) *New Engl. J. Med.* 348:601-608; Milgrom *et al.* (1999) *New Engl. J. Med.* 341:1966-1973; Slamon *et al.* (2001) *New Engl. J. Med.* 344:783-792; Beniaminovitz *et al.* (2000) *New Engl. J. Med.* 342:613-619; Ghosh *et al.* (2003) *New Engl. J. Med.* 348:24-32; Lipsky *et al.* (2000) *New Engl. J. Med.* 343:1594-1602).

[00167] Determination of the appropriate dose is made by the clinician, *e.g.*, using parameters or factors known or suspected in the art to affect treatment. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved relative to any negative side effects. Important diagnostic measures include those of symptoms of, *e.g.*, the inflammation or level of inflammatory cytokines produced. In general, it is desirable that a biologic that will be used is derived from the same species as the animal targeted for treatment, thereby minimizing any immune response to the reagent. In the case of human subjects, for example, chimeric, humanized and fully human antibodies may be desirable.

[00168] Antibodies or antigen binding fragments thereof can be provided by continuous infusion, or by doses administered, e.g., daily, 1-7 times per week, weekly, bi-weekly, monthly, bimonthly, quarterly, semiannually, annually etc. Doses may be provided, e.g., intravenously, subcutaneously, topically, orally, nasally, rectally, intramuscular, intracerebrally, intraspinally, or by inhalation. A total weekly dose is generally at least 0.05 µg/kg body weight, more generally at least 0.2 µg/kg, 0.5 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 0.25 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 5.0 mg/ml, 10 mg/kg, 25 mg/kg, 50 mg/kg or more (see, e.g., Yang, et al. (2003) *New Engl. J. Med.* 349:427-434; Herold, et al. (2002) *New Engl. J. Med.* 346:1692-1698; Liu, et al. (1999) *J. Neurol. Neurosurg. Psych.* 67:451-456; Portielji, et al. (20003) *Cancer Immunol. Immunother.* 52:133-144). Doses may also be provided to achieve a pre-determined target concentration of the antibody in the subject's serum, such as 0.1, 0.3, 1, 3, 10, 30, 100, 300 µg/ml or more. In other embodiments, a fully human antibody is administered subcutaneously or intravenously, on a weekly, biweekly, "every 4 weeks," monthly, bimonthly, or quarterly basis at 10, 20, 50, 80, 100, 200, 500, 1000 or 2500 mg/subject or as otherwise provided for herein.

[00169] As used herein, "inhibit" or "treat" or "treatment" includes a postponement of development of the symptoms associated with a disorder and/or a reduction in the severity of the symptoms of such disorder. The terms further include ameliorating existing uncontrolled or unwanted symptoms, preventing additional symptoms, and ameliorating or preventing the underlying causes of such symptoms. Thus, the terms denote that a beneficial result has been conferred on a vertebrate subject with a disorder, disease or symptom, or with the potential to develop such a disorder, disease or symptom.

[00170] As used herein, the terms "therapeutically effective amount", "therapeutically effective dose" and "effective amount" refer to an amount of the antibody, or antigen binding fragment thereof, that, when administered alone or in combination with an additional therapeutic agent to a cell, tissue, or subject, is effective to cause a measurable improvement in one or more symptoms of a disease or condition or the progression of such disease or condition. A therapeutically effective dose further refers to that amount of the binding compound sufficient to result in at least partial amelioration of symptoms, e.g., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to

combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. An effective amount of a therapeutic will result in an improvement of a diagnostic measure or parameter by at least 10%; usually by at least 20%; preferably at least 30%; more preferably at least 40%, and most preferably by at least 50%. An effective amount can also result in an improvement in a subjective measure in cases where subjective measures are used to assess disease severity. In some embodiments, an amount is a therapeutically effective amount if it is an amount that can be used to treat or ameliorate a condition as provided for herein.

[00171] The term “subject” as used throughout includes any organism, such as an animal, including a mammal (*e.g.*, rat, mouse, dog, cat, rabbit) and, for example, a human. A subject can also be referred to as a patient. In some embodiments, the subject is a subject in need thereof. A subject that is “in need thereof” refers to a subject that has been identified as requiring treatment for the condition that is to be treated and is treated with the specific intent of treating such condition. The conditions can be, for example, any of the conditions described herein.

[00172] Whereas an isolated antibody binds an epitope on an IGF-1R protein, or other protein described herein, and displays *in vitro* and/or *in vivo* IGF-1R inhibiting or therapeutic activities, the antibodies or antigen binding fragments thereof, capable of inhibiting IGF-1R function, are suitable both as therapeutic agents for treating IGF-1R -associated conditions in humans and animals. These conditions include thyroid eye disease. According, methods of treating such conditions are also provided, wherein the method comprises administering an antibody, or antigen binding fragment thereof, to the subject with such a condition.

[00173] In some embodiments, the methods comprise administering a therapeutically or prophylactically effective amount of one or more monoclonal antibodies or antigen binding fragments of the antibodies described herein to a susceptible subject or to one exhibiting a condition in which IGF-1R is known or suspected to have caused the pathology observed. Any active form of the antibody can be administered, including, but not limited to scFV, Fab and F(ab')₂ fragments and other forms of antibodies provided for herein.

[00174] As used herein, an IGF-1R associated pathology refers to conditions that are caused by the modulation of IGF-1R. These conditions include, but are not limited to, thyroid eye disease and other conditions provided for herein. In some embodiments, the thyroid eye disease is acute thyroid eye disease. In some embodiments, the thyroid eye disease is chronic thyroid eye disease.

[00175] In some embodiments, the antibodies used are compatible with the recipient species such that the immune response to the MAbs does not result in an unacceptably short circulating half-life or induce an immune response to the MAbs in the subject.

[00176] Treatment of individuals may comprise the administration of a therapeutically effective amount of the antibodies described herein. The antibodies can be provided in a kit, such as those provided herein. The antibodies can be used or administered alone or in admixture with another therapeutic, analgesic, or diagnostic agent, such as provided for herein. In providing a patient with an antibody, or fragment thereof, capable of binding to IGF-1R, or an antibody capable of protecting against IGF-1R pathology in a recipient patient, the dosage of administered agent will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition, previous medical history, etc.

[00177] An antibody, capable treating a condition associated with IGF-1R activity or use to treat an IGF-1R related pathology, is intended to be provided to subjects in an amount sufficient to affect a reduction, resolution, or amelioration in the IGF-1R related symptom or pathology. Such a pathology includes thyroid eye disease and the like.

[00178] Accordingly, in some embodiments, methods of treating a subject with an IGF-1R mediated disorder are provided. In some embodiments, the method comprises administering a pharmaceutical composition comprising an antibody, or antigen binding fragment thereof, as provided herein. In some embodiments, the disorder is thyroid eye disease. As provided for herein, the antibodies, or antigen binding fragments thereof, can be administered with other therapeutics. These can be administered simultaneously or sequentially.

[00179] In some embodiments, the antibodies, or antigen binding fragments thereof, may be used to treat thyroid eye disease. In some embodiments, the antibodies, or antigen binding fragments thereof, may be used to treating or reduce the severity of, thyroid-associated ophthalmopathy (TAO), or a symptom thereof.

[00180] In some embodiments, methods or uses are provided to reduce proptosis in an eye in a subject with thyroid-associated ophthalmopathy (TAO).

[00181] In some embodiments, the subject is a subject how has previously been treated with a different antibody than those provided herein.

[00182] In some embodiments, methods or uses are provided to Clinical Activity Score (CAS) in subject who has or is suspected of having thyroid-associated ophthalmopathy (TAO).

[00183] In some embodiments, methods or uses are provided to reduce proptosis by at least 2 mm. In some embodiments, methods or uses are provided to reduce proptosis by at least 3 mm. In some embodiments, methods or uses are provided to reduce proptosis by at least 2-3 mm or 2-4 mm. In some embodiments, the proptosis is reduced by at least 2, 3, or 4 mm. In some embodiments, the reduction in proptosis is seen within 3 weeks of the first dose administration. In some embodiments, the reduction in proptosis is seen within 6 weeks of the first dose administration.

[00184] In some embodiments, the subject has a reduced the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO).

[00185] As used herein, the term Clinical Activity Score (CAS) refers to the protocol described and scored according to **Table 2**. According to this protocol, one point is given for the presence of each of the parameters assessed in **Table 2** below. The sum of all points defines clinical activity and provides the CAS, where 0 or 1 constitutes inactive disease and 7 severe active ophthalmopathy.

Table 2	
Parameters for calculating Clinical Activity Score	
Item No.	Parameter
1	Spontaneous retrobulbar pain
2	Pain on attempted eye movements (upward, side to side, and downward gazes; sometimes termed gaze evoked orbital pain)
3	Eyelid swelling
4	Eyelid erythema (redness)
5	Conjunctival redness
6	Chemosis (swelling/edema of the conjunctiva)
7	Swelling of caruncle or pila

[00186] As provided in **Table 2**, the CAS consists of seven components: spontaneous retrobulbar pain, pain on attempted eye movements (upward, side-to-side, and downward gazes), conjunctival redness, redness of the eyelids, chemosis, swelling of the caruncle/plica, and swelling of the eyelids. Each component is scored as present (1 point) or absent (0 points). The score at each efficacy assessment is the sum of all items present; giving a range of 0-7, where 0 or 1 constitutes inactive disease and 7 severe active ophthalmopathy. A change of >2

points is considered clinically meaningful. In some embodiments, the subject's score improves by at least 2, 3, or 4 points. In some embodiments, the subject's score improves within 3 weeks of the first dose. In some embodiments, the subject's score improves within 6 weeks of the first dose.

[00187] Item 1, spontaneous orbital pain could be a painful, or oppressive feeling on, or behind, the globe. This pain may be caused by the rise in intraorbital pressure, when the orbital tissues volume increases through excess synthesis of extracellular matrix, fluid accumulation, and cellular infiltration and expansion. Item 2, gaze evoked orbital pain, could be pain in the eyes when looking, or attempting to look, up, down or sideways, i.e., pain with upward, downward, or lateral eye movement, or when attempting eye movement. This kind of pain could arise from the stretching of the inflamed muscle(s), especially on attempted upgaze. The 'stretching pain' cannot be provoked by digital pressing on the eyeball, as would be expected if it were a manifestation of the raised intraorbital pressure. Both kinds of pain can be reduced after anti-inflammatory treatment. These kinds of pain are therefore considered to be directly related to autoimmune inflammation in the orbit and thus useful in assessing TAO activity.

[00188] Swelling in TAO is seen as chemosis (edema of the conjunctiva), item no. 6 in **Table 2**, and swelling of the caruncle and/or plica semilunaris. Both are signs of TAO activity. Swollen eyelids can be caused by edema, fat prolapse through the orbital septum, or fibrotic degeneration. In addition to swelling, other symptoms indicative of active TAO include redness and/or pain of the conjunctiva, eyelid, caruncle and/or plica semilunaris.

[00189] In some embodiments, the subject who is treated has the proptosis is reduced by at least 2 mm. In some embodiments, the subject who is treated has the proptosis is reduced by at least 3 mm. In some embodiments, the subject who is treated has the proptosis is reduced by at least 4 mm.

[00190] In some embodiments, in the subjects who are treated the clinical activity score (CAS) of the subject is reduced by at least 2 points. In some embodiments, the clinical activity score (CAS) of the subject is reduced to one (1). In some embodiments, the clinical activity score (CAS) of the subject is reduced to zero (0).

[00191] In some embodiments, methods off treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) in a subject are provided, wherein the treatment with said antibody (i) reduces proptosis by at least 2 mm in an eye; (ii) is not accompanied by a deterioration of 2 mm or more in the other (or fellow eye); and (iii) reduces the CAS in said subject to either one (1) or zero (0).

[00192] In some embodiments, methods of improving the quality of life in a subject with thyroid-associated ophthalmopathy (TAO, also called Graves' Ophthalmopathy/Graves' Orbitopathy) are provided. In some embodiments, the quality of life is measured by the Graves' Ophthalmopathy Quality of Life (GO-QoL) assessment, or either the Visual Functioning or Appearance subscale thereof. In some embodiments, the treatment results in an improvement of greater than or equal to 8 points on the GO-QoL. In some embodiments, the treatment results in an improvement on the Functioning subscale of the GO-QoL. In some embodiments, the treatment results in an improvement on the Appearance subscale of the GO-QoL.

[00193] In some embodiments, methods of treating or reducing the severity of diplopia in a subject with thyroid-associated ophthalmopathy (TAO) are provided. In some embodiments, the diplopia is constant diplopia. In some embodiments, the diplopia is inconstant diplopia. In some embodiments, the diplopia is intermittent diplopia. In some embodiments, the improvement in or reduction in severity of diplopia is sustained at least 20 weeks after discontinuation of antibody administration. In some embodiments, the improvement in or reduction in severity of diplopia is sustained at least 50 weeks after discontinuation of antibody administration. In some embodiments, the diplopia is improved in the subject within 3 weeks or within 6 weeks of the first dose.

[00194] The severity of the disease can be measured in the following non-limiting embodiments. For example, for lid aperture, the distance between the lid margins are measured (in mm) with the patient looking in the primary position, sitting relaxed, and with distant fixation. For swelling of the eyelids, the measure/evaluation is either "absent/equivocal," "moderate," or "severe." Redness of the eyelids is either absent or present. Redness of the conjunctivae is either absent or present. In some embodiments, conjunctival edema is either absent or present. In some embodiments, inflammation of the caruncle or plica is either absent or present. Exophthalmos is measured in millimeter using the same Hertel exophthalmometer and same intercanthal distance for an individual patient. Subjective diplopia is scored from 0 to 3 (0=no diplopia; 1=intermittent, i.e., diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e., diplopia at extremes of gaze; 3=constant, i.e., continuous diplopia in primary or reading position). For eye muscle involvement, the ductions are measured in degrees. Corneal involvement is either absent/punctate or keratopathy/ulcer. For optic nerve involvement, i.e., best-corrected visual acuity, color vision, optic disc, relative afferent pupillary defect, the condition is either absent

or present. In addition, visual fields are checked if optic nerve compression is suspected. In some embodiments, the patient can be classified according to the following severity classification. For example, sight-Threatening Thyroid Eye Disease: Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention. Moderate-to-Severe Thyroid Eye Disease: Patients without sight-threatening disease whose eye disease have sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate-to-severe thyroid eye disease usually have any one or more of the following: lid retraction greater than or equal to 2 mm, moderate or severe soft tissue involvement, exophthalmos greater than or equal to 3 mm above normal for race and gender, inconstant or constant diplopia. Mild Thyroid Eye Disease: Patients whose features of thyroid eye disease have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

[00195] In some embodiments, a patient can be characterized by Graves Ophthalmopathy Quality of Life (GO-QoL) score. In addition to proptosis (or exophthalmos) and CAS, quality of life is also evaluated with the use of the GO quality of life (GO-QoL) questionnaire. This questionnaire is designed to determine the improved quality of life after treatment with a method disclosed herein. In some embodiments, questionnaire may determine the decreased or lack of side effects after being treated with an antibody, or an antigen binding fragment thereof, according to a method disclosed herein as compared to treatment with glucocorticoids. The GO-QoL is a 16-item self-administered questionnaire divided into 2 subsets and used to assess the perceived effects of TED by the subjects on (i) their daily physical activity as it relates to visual function, and (ii) psychosocial functioning. quality of life is evaluated with the use of the GO QoL questionnaire. The GO-QoL questionnaire [C. B. Terwee et al, 1998] is completed on Day 1 and Weeks 6, 12, and 24 (or PW) during the Treatment Period, and at Months 7 and 12 (or PW) during the Follow-Up Period. The GO-QoL is a 16-item self-administered questionnaire divided into two self-assessment subscales; one covering impact of visual function on daily activities, the other assesses the impact of self-perceived appearance. The visual function subscale covers activities such as driving, walking outdoors, reading, watching television. The appearance subscale asks the subject questions such as whether ophthalmopathy has altered the subject's appearance, caused other people to

have a negative reaction to the subject, caused social isolation, and caused the subject to try to mask his or her appearance. Each subscale has 8 questions which are answered with: yes--very much so; yes--a little; or no--not at all. Each question is scored 0-2, respectively, and the total raw score is then mathematically transformed to a 0-100 scale, where 0 represents the most negative impact on quality of life, and 100 represents no impact. A change of ≥ 8 points on the 0-100 scale has been shown to be clinically meaningful. The combined score takes raw scores from both subscales and again transforms them to a single 0-100 scale. The questionnaire has two self-assessment subscales. Each subscale has 8 questions which are answered with: (i) yes--very much so; (ii) yes--a little; or (iii) no--not at all. Each question is scored 0-2, respectively, and the total raw score is then mathematically transformed to a 0-100 scale, where 0 represents the most negative impact on quality of life, and 100 represents no impact. A change of ≥ 8 points on the 0-100 scale is considered to be clinically meaningful. The combined score takes raw scores from both subscales and again transforms them to a single 0-100 scale.

[00196] Patients can also be assessed by the presence or absence of Gorman Grading of Diplopia. The Gorman assessment of subjective diplopia includes four categories: no diplopia (absent), diplopia when the patient is tired or awakening (intermittent), diplopia at extremes of gaze (inconstant), and continuous diplopia in the primary or reading position (constant). Patients are scored according to which grade of diplopia they are experiencing. An improvement of greater than equal or to 1 grade is considered clinically meaningful.

[00197] In some embodiments, methods described herein can treat fibrosis (e.g., ocular fibrosis). In some embodiments, a therapeutic benefit is an alleviation of fibrosis (e.g., ocular fibrosis). In some embodiments, a therapeutic benefit is a reversal in fibrosis (e.g., ocular fibrosis). In some embodiments, a therapeutic benefit is prevention of fibrosis or prevention of further fibrosis (e.g., ocular fibrosis). In some embodiments, a therapeutic benefit from alleviation and/or reversal in ocular fibrosis is improvement in vision. In some embodiments, a therapeutic benefit from alleviation and/or reversal in ocular fibrosis is no further deterioration in vision or no worsening of symptoms (e.g., preservation of vision or no further vision loss or impairment). In embodiments, treatment of ocular fibrosis results in improvements in diplopia and/or proptosis (e.g., as described herein). In embodiments, the fibrosis (e.g., ocular fibrosis) is associated with or results from inflammation. In embodiments, the fibrosis (e.g., ocular fibrosis) is associated with or results from an autoimmune disorder. In embodiments, the fibrosis (e.g., ocular fibrosis) is associated with or results from thyroid eye disease. In

embodiments, ocular fibrosis is fibrosis that develops around the extraocular muscles. In some embodiments, the fibrosis (e.g., ocular fibrosis) follows an inflammatory period of TED (e.g., fibrosis following active TED or following an inflammatory flare-up in a patient having chronic and/or inactive TED). One skilled in the art will appreciate that a variety of methods well-known in the art may be used to assess changes in fibrosis (e.g., ocular fibrosis), including biopsy followed by staining or via imaging techniques (e.g., computed tomography (CT) or magnetic resonance imaging (MRI)). Still other methods of diagnosing and/or characterizing fibrosis (e.g., ocular fibrosis) include dye-based angiography, optical coherence tomography (OCT), and OCT angiography (OCTA). Fibrosis may also be assessed using levels of inflammatory or fibrotic factors. In some embodiments, the fibrosis is assessed through one or more of analysis of adenosine monophosphate-activated protein kinase (AMPK), fibronectin, alpha-SMA, and collagen staining.

[00198] In some embodiments, a subject is an adult with an age of ≥ 18 years. In some embodiments, a subject is an adult with an age of ≤ 75 years of age. In some embodiments, a subject is an adult with an age of between 18 and 75 years. In some embodiments, a subject is male. In some embodiments, a subject is female.

[00199] In some embodiments, a subject has a body weight of ≤ 200 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 180 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 175 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 170 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 160 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 150 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 130 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 125 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 120 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 110 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 100 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 90 kilograms (kg). In some embodiments, a subject has a body weight of ≤ 80 kilograms (kg).

[00200] In some embodiments, a subject has a clinical diagnosis of TED with a CAS of >0 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of ≥ 1 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of ≥ 2 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of ≥ 3 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of

≥ 4 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of ≥ 5 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of ≥ 6 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 1 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 2 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 3 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 4 on the 5-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 6 on the 7-item scale for study eye. In some embodiments, a subject has a clinical diagnosis of TED with a CAS of 7 on the 7-item scale for study eye.

[00201] In some embodiments, a subject has moderate to severe (i.e., has an appreciable impact on daily living) active TED associated with proptosis of ≥ 3 mm above normal values for race and gender, and ≥ 17 mm at pre-dose baseline (Day 1), and at least one additional sign/symptom. In some embodiments, a subject has moderate active TED. In some embodiments, a subject has severe TED.

[00202] In some embodiments, a subject has proptosis of ≥ 1 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 2 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 3 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 4 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 5 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 6 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 7 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 8 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 9 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 10 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 11 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 12 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 13 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 14 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 15 mm above normal values for race and gender. In some embodiments, a subject has proptosis of $\geq$

16mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 17 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 18 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 19 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 20 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 21 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 22 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 23 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 24 mm above normal values for race and gender. In some embodiments, a subject has proptosis of ≥ 25 mm above normal values for race and gender.

[00203] In some embodiments, a subject has proptosis of ≥ 1 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 2 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 3 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 4 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 5 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 6 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 7 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 8 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 9 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 10 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 11 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 12 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 13 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 14 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 15 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 16 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 17 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 18 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 19 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 20 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 21 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 22 mm at pre-dose baseline (Day 1). In some

embodiments, a subject has proptosis of ≥ 23 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 24 mm at pre-dose baseline (Day 1). In some embodiments, a subject has proptosis of ≥ 25 mm at pre-dose baseline (Day 1).

[00204] In some embodiments, a subject has proptosis of ≥ 1 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 2 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 3 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 4 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 5 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 6 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 7 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 8 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 9 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 10 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 11 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 12 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 13 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 14 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 15 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 16 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 17 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 18 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 19 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 20 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 21 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some

embodiments, a subject has proptosis of ≥ 22 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 23 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 24 mm at pre-dose baseline (Day 1) measured by exophthalmometer. In some embodiments, a subject has proptosis of ≥ 25 mm at pre-dose baseline (Day 1) measured by exophthalmometer.

[00205] In some embodiments, a subject has proptosis of ≥ 1 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 2 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 3 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 4 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 5 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 6 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 7 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 8 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 9 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 10 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 11 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 12 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 13 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 14 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 15 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 16 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 17 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 18 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 19 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 20 mm at pre-dose baseline (Day 1) measured by

MRI/CT. In some embodiments, a subject has proptosis of ≥ 21 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 22 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 23 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 24 mm at pre-dose baseline (Day 1) measured by MRI/CT. In some embodiments, a subject has proptosis of ≥ 25 mm at pre-dose baseline (Day 1) measured by MRI/CT.

[00206] In some embodiments, a subject has proptosis of ≥ 1 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 2 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 3 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 4 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 5 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 6 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 7 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 8 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 9 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 10 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 11 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 12 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 13 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 14 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 15 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 16 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by

MRI/CT. In some embodiments, a subject has proptosis of ≥ 17 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 18 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 19 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 20 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 21 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 22 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 23 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 24 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT. In some embodiments, a subject has proptosis of ≥ 25 mm at pre-dose baseline (Day 1) measured by exophthalmometer and by MRI/CT.

[00207] In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 15 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED.

[00208] In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 14 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 13 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 12 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 11 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 10 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 9 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 8 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with

active TED that began within 7 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 6 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 5 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 4 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 3 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 2 months prior to study screening. In some embodiments, a subject has documented evidence of ocular symptoms or signs associated with active TED that began within 1 months prior to study screening.

[00209] In some embodiments, a subject is a female who has a negative serum pregnancy test at screening.

[00210] In some embodiments, a subject does not have prior treatment with another anti-IGF-1R therapy. In some embodiments, a subject has not used systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study medication drug. In some embodiments, a subject has not received periocular (including intraorbital) or intraocular administration of steroids within 3 months prior to the first dose of study medication drug.

[00211] In some embodiments, a subject has not received other immunosuppressive agents within 16 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 15 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 14 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 13 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 12 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 11 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 10 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 9 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 8 weeks prior

to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 7 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 6 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 5 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 4 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 3 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 2 weeks prior to the first dose of study. In some embodiments, a subject has not received other immunosuppressive agents within 1 week prior to the first dose of study.

[00212] In some embodiments, an immunosuppressive agent is rituximab. In some embodiments, an immunosuppressive agent is tocilizumab. In some embodiments, an immunosuppressive agent is secukimumab. In some embodiments, an immunosuppressive agent is satralizumab. In some embodiments, an immunosuppressive agent is an anti-FcRn. In some embodiments, an immunosuppressive agent is any other therapy for TED.

[00213] In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 16 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 15 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 14 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 13 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 12 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 11 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 10 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 9 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 8 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 7 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 6 weeks prior to the first dose of study drug. In some embodiments, a subject

has not received radioactive iodine (RAI) treatment within 5 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 4 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 3 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 2 weeks prior to the first dose of study drug. In some embodiments, a subject has not received radioactive iodine (RAI) treatment within 1 week prior to the first dose of study drug.

[00214] In some embodiments, a subject has not received previous orbital irradiation or decompression surgery involving excision of fat for TED to the study eye's orbit.

[00215] In some embodiments, a subject does not have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future.

[00216] In some embodiments, a subject does not have corneal decompensation in the study eye unresponsive to medical management.

[00217] In some embodiments, a subject does not abnormal baseline audiometry or history of significant ear pathology, relevant ear surgery, hearing impairment or hearing loss.

[00218] In some embodiments, a subject does not have an inflammatory bowel disease.

[00219] In some embodiments, a subject is not a pregnant woman. In some embodiments, a subject is not a lactating woman.

[00220] In some embodiments, the methods comprise administering an antibody, such as those provided herein. In some embodiments, the antibody is administered at a dosage of 1 mg/kg to 5 mg/kg antibody as a first dose. In some embodiments, the antibody is administered at a dosage of 5 mg/kg to 10 mg/kg antibody as a first dose. In some embodiments, the antibody is administered at a dosage of 5 mg/kg to 20 mg/kg antibody in subsequent doses. In some embodiments, the antibody is administered in the following amounts: 10 mg/kg antibody as a first dose; and 20 mg/kg antibody in subsequent doses. In some embodiments, the subsequent doses are administered every three weeks for at least 21 weeks.

[00221] In some embodiments, the antibody is administered in a pharmaceutical composition, such as those provided herein. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically active compounds for the treatment of TAO. In some embodiments, the pharmaceutical composition further comprises corticosteroids; rituximab or other anti-CD20 antibodies; tocilizumab or other anti-IL-6

antibodies; or selenium, or infliximab or other anti-TNFalpha antibodies or a thyroid-stimulating hormone receptor (TSHR) inhibitor.

[00222] In some embodiments, the method provided herein comprise administering to a subject an antibody, or an antigen binding fragment thereof, that specifically binds to and inhibits IGF-1R. In some embodiments, the antibody is as provided herein.

[00223] Kits are also provided which are useful for carrying out embodiments described herein. The present kits comprise a first container containing or packaged in association with the above-described antibodies. The kit may also comprise another container containing or packaged in association solutions necessary or convenient for carrying out the embodiments. The containers can be made of glass, plastic or foil and can be a vial, bottle, pouch, tube, bag, etc. The kit may also contain written information, such as procedures for carrying out the embodiments or analytical information, such as the amount of reagent contained in the first container means. The container may be in another container apparatus, e.g. a box or a bag, along with the written information.

[00224] Yet another aspect provided for herein is a kit for detecting IGF-1R protein in a biological sample. The kit includes a container holding one or more antibodies which binds an epitope of IGF-1R protein and instructions for using the antibody for the purpose of binding to IGF-1R protein to form an immunological complex and detecting the formation of the immunological complex such that the presence or absence of the immunological complex correlates with presence or absence of IGF-1R protein in the sample. Examples of containers include multiwell plates which allow simultaneous detection of IGF-1R protein in multiple samples.

[00225] In some embodiments, antibodies that bind to an IGF-1R protein are provided. In some embodiments, the antibody is isolated. In some embodiments, the antibody binds specifically. In some embodiments, the antibody binds to an IGF-1R protein that is properly folded. In some embodiments, the antibody is specific for a specific IGF-1R conformational state (open or closed). In some embodiments, the antibody binds to an IGF-1R protein in a cell membrane. In some embodiments, the antibody binds to an IGF-1R protein that is in a cell membrane in an intact cell. In some embodiments, the antibody inhibits or neutralizes the function of an IGF-1R protein. As used herein, the term "neutralize" means that the activity or function of the protein is inhibited. The inhibition can be complete or partial. In some embodiments, the activity or function of the protein is inhibited at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95, or 99%. The percent inhibition can be based upon the function or activity of the

protein in the absence of the antibody. In some embodiments, the antibody inhibits the glucose transport facilitated by IGF-1R. In some embodiments, the antibody inhibits the internalization of the IGF-1R protein.

[00226] In some embodiments, the antibody comprises a sequence as provided for herein or antigen binding fragment thereof. In some embodiments, the antibody comprises a heavy chain CDR or an antigen binding fragment thereof described herein. The heavy chain may be one or more of the heavy chains described herein. In some embodiments, the antibody comprises a light chain, or an antigen binding fragment thereof as described herein

[00227] In some embodiments, methods of treating, inhibiting or ameliorating an IGF-1R, associated pathology are provided. In some embodiments, the methods comprise administering an antibody described herein or a pharmaceutical composition described herein to a subject to treat, inhibit or ameliorate an IGF-1R associated pathology. In some embodiments, the pathology is as described herein.

[00228] In some embodiments, methods of detecting the presence or absence of an IGF-1R in a sample are provided, the method comprising contacting a sample with one or more antibodies described herein detecting the binding to an IGF-1R antigen by the antibody. In some embodiments, the detection of the binding indicates the presence IGF-1R antigen; or the absence of the detection of the binding to the IGF-1R antigen indicates the absence of the IGF-1R antigen. The detecting can be done with any known method, such as using a biosensor, ELISA, sandwich assay, and the like. However, in some embodiments, the method comprises detecting the presence of the protein in non-denaturing conditions. The non-denaturing conditions can be used so that the protein of interest is detected in its native, or properly folded form.

[00229] In some embodiments, methods of identifying a test antibody that binds to an epitope on IGF-1R protein, are provided, the method comprising contacting a test antibody with the epitope on IGF-1R protein and determining whether the test antibody binds to the epitope. In some embodiments, the determining comprises determining whether the test antibody binds to the protein and is competitively inhibited by an antibody comprising a sequence as provided herein. In some embodiments, the determining comprises mutating one or more residues of epitope or protein and determining binding of the test antibody to the mutated epitope, wherein if the mutation reduces binding of the test antibody as compared to the non-mutated epitope, the test antibody is deemed to bind to that epitope.

[00230] In some embodiments, methods of monitoring internalization of IGF-1R from the surface of a cell are provided. In some embodiments, the method comprising contacting the cell with an anti- IGF-1R antibody as provided herein and detecting the presence of IGF-1R in the cell or on the surface of the cell. The differences in cell surface expression can be measured and the internalization can be monitored and measured. This can be used, for example, to measure the effect of another molecule, such as a test agent, to modulate internalization of IGF-1R protein. Thus, the antibodies provided for herein can be used to identify test agents that modulate (increase or decrease) the internalization of IGF-1R protein. Test molecules that increase the internalization, which would be measured as a decrease in binding of an anti- IGF-1R antibody to IGF-1R protein on the cell surface, can be identified according to the methods provided herein. Test molecules that decrease the internalization, which would be measured as an increase in binding of an anti- IGF-1R antibody to IGF-1R protein on the cell surface, can be identified according to the methods provided herein. The surface expression can be measured by fluorescence, which can be done through a secondary antibody that recognized the IGF-1R antibodies or by labelling the anti- IGF-1R antibodies provided for herein.

[00231] In some embodiments, an antibody for use in the treatment of thyroid associated ophthalmopathy in a subject in need thereof, is provided. In some embodiments, an anti-IGF-1R antibody for use in the treatment of thyroid associated ophthalmopathy in a subject in need thereof, is provided.

[00232] In some embodiments, methods of treating a patient with chronic thyroid eye disease are provided. In some embodiments, the patient has moderate to severe, thyroid eye disease. In some embodiments, the patient with chronic thyroid eye disease has had symptoms for at least 1 year. In some embodiments, the patient with chronic thyroid eye disease has had symptoms for at least 15 months. In some embodiments, the patient with chronic thyroid eye disease has had symptoms for more than one year. In some embodiments, the patient, prior to administration of a first dose of a pharmaceutical composition provided for herein, has had symptoms of thyroid eye disease more than 2, 3, 4, 5, 6, or 7 years, or 1 to 8 years, 1 to 7 years, 1 to 6 years, 1 to 5 years, 1 to 4 years, 1 to 3 years, 1 to 2 years, 2 to 8 years, 2 to 7 years, 2 to 6 years, 2 to 5 years, 2 to 4 years, 2 to 3 years, 3 to 8 years, 3 to 7 years, 3 to 5 years, 3 to 4 years, 4 to 8 years, 4 to 7 years, 4 to 6 years, 4 to 5 years, 5 to 8 years, 5 to 7 years, 5 to 6 years, 6 to 8 years, 6 to 7 years, or 7 to 8 years. In some embodiments, the patient, prior to administration a dose of a pharmaceutical composition provided for herein, has had symptoms

of thyroid eye disease no more than 63 months, 60 months, 48 months, 36 months, 24 months, 15 months, 13 months, or 12 months. In some embodiments, the patient prior to administration a dose of a pharmaceutical composition provided for herein, has had symptoms of thyroid eye disease no more than 15 months.

[00233] In some embodiments, the patient, prior to administration of a first dose of a pharmaceutical composition provided for herein, has had symptoms of thyroid eye disease for at least or greater than one year and has one or more of the following symptoms of thyroid eye disease: lid retraction greater than 2mm; exophthalmos (proptosis) of greater than or equal to 3 mm; Clinical Activity Score (CAS) from 0 to 7; inconstant or constant diplopia, or any combination thereof. In some embodiments, the exophthalmos is greater than or equal to 3 mm above the normal range for their race and gender. In some embodiments, the patient has exophthalmos that is greater than or equal to 3 mm and a CAS from 0 to 7. In some embodiments, the patient has a CAS greater than or equal to 2. In some embodiments, the patient has a CAS greater than or equal to 3. In some embodiments, the patient has a CAS greater than or equal to 4. In some embodiments, the patient has a CAS greater than or equal to 5. In some embodiments, the patient has a CAS greater than or equal to 6. In some embodiments, the patient has a CAS equal to 7. In some embodiments, the patient has a CAS greater than or equal to 3 and the patient, prior to administration a dose of a pharmaceutical composition provided for herein, has had symptoms of thyroid eye disease no more than 15 months.

[00234] As provided for herein, in some embodiments, the pharmaceutical composition is administered by infusion, intravenously, or subcutaneously. In some embodiments, the composition is administered intravenously, such as by infusion.

[00235] In some embodiments, the proptosis in the subject with chronic thyroid eye disease is reduced by 1 to 3 mm, 1 to 2 mm, 2 to 3 mm from baseline as measured by exophthalmometry or by MRI/CT. In some embodiments, the proptosis is reduced by 2-3 mm from baseline as measured by exophthalmometry or by MRI/CT. In some embodiments, the reduction is seen within 6 or at 6 weeks after administration of the first dose. In some embodiments, the reduction is seen after 2 doses are administered. In some embodiments, the dose is 3 mg/kg or 10 mg/kg, or other doses as provided for herein. In some embodiments, each of the doses that are administered to the patient are the same.

[00236] In some embodiments, the subject, prior to administration of the pharmaceutical composition, had a CAS of greater than 0, 1, 2, 3, or 4, or 2 to 4. In some embodiments, the

subject, prior to administration of the pharmaceutical composition, had a CAS of greater than or equal to 2, 3, or 4. In some embodiments, the subject, prior to administration of the pharmaceutical composition, had a CAS of greater than or equal to 2. In some embodiments, the subject, prior to administration of the pharmaceutical composition, had a CAS of greater than or equal to 3. In some embodiments, the subject, prior to administration of the pharmaceutical composition, had a CAS of greater than or equal to 4.

[00237] In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1 mm to -2 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1.2 mm to -2 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1.3 mm to -2 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1.4 mm to -2 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1.5 mm to -2 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis from -1.3 mm to -1.8 mm. In some embodiments, a patient with chronic TED and a CAS of 0 or 1 has a reduction in proptosis of -1.1 mm, -1.2 mm, -1.3 mm, -1.4 mm, -1.5 mm, -1.6 mm, -1.7 mm, -1.8 mm, -1.9 mm, or -2.0 mm. In some embodiments, the reduction occurs within 6 weeks of the administration of the first dose. In some embodiments, the reduction occurs after 2 doses are administered to the patient. In some embodiments, the dose is as provided for herein. In some embodiments, each of the doses that are administered to the patient are the same. In some embodiments, the initial dose is a loading dose that is higher than subsequent (maintenance) doses. The loading dose can be administered as a single dose or combination of doses that are administered simultaneously or nearly simultaneously, i.e., the same day. In some embodiments, the loading dose is administered over 2 days. Regardless of how many doses are administered as a loading dose, it should be understood that the loading dose is considered a single dose for the purpose of counting total doses that a subject is administered. For example, if a patient is scheduled to receive 5 doses of a pharmaceutical composition over a period of weeks and/or months as provided for herein and the administration includes a loading dose and maintenance dose, and the loading dose is given as more than one dose, such as two, those two doses only count as single dose of the 5 dose administration and 4 subsequent maintenance doses would be still be administered to give the subject a total of “5 doses.”

[00238] As provided for herein, methods of treating thyroid eye disease in a subject are provided. In some embodiments, the methods comprise administering to the subject subcutaneously a pharmaceutical composition comprising a therapeutically effective amount of an anti-IGF-1R antibody.

[00239] In some embodiments, the therapeutically effective amount is 100 mg to 1000 mg, 200 mg to 1000 mg, 300 mg to 1000 mg, 400 mg to 1000 mg, 500 mg to 1000 mg, 600 mg to 1000 mg, 700 mg to 1000 mg, 800 mg to 1000 mg, 900 mg to 1000 mg, 100 mg to 900 mg, 100 mg to 800 mg, 100 mg to 700 mg, 100 mg to 600 mg, 100 mg to 500 mg, 100 mg to 400 mg, 100 mg to 300 mg, 100 mg to 200 mg, 200 mg to 1000 mg, 200 mg to 900 mg, 200 mg to 800 mg, 200 mg to 700 mg, 200 mg to 600 mg, 200 mg to 500 mg, 200 mg to 400 mg, 200 mg to 300 mg, 300 mg to 1000 mg, 300 mg to 900 mg, 300 mg to 800 mg, 300 mg to 700 mg, 300 mg to 600 mg, 300 mg to 500 mg, 300 mg to 400 mg, 400 mg to 1000 mg, 400 mg to 900 mg, 400 mg to 800 mg, 400 mg to 700 mg, 400 mg to 600 mg, 400 mg to 500 mg, 500 mg to 1000 mg, 500 mg to 900 mg, 500 mg to 800 mg, 500 mg to 700 mg, 500 mg to 600 mg, 600 mg to 1000 mg, 600 mg to 900 mg, 600 mg to 800 mg, 600 mg to 700 mg, 700 mg to 1000 mg, 700 mg to 900 mg, 700 mg to 800 mg, 800 mg to 1000 mg, 800 mg to 900 mg, 900 mg to 1000 mg, 250 mg to 750 mg, 250 mg to 700 mg, 250 mg to 650 mg, 700 mg to 600 mg, 300 mg to 750 mg, 300 mg to 700 mg, 300 mg to 650 mg, 300 mg to 600 mg, 250 mg to 350 mg, 275 mg to 325 mg, 550 to 650 mg, 575 to 625 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, or 700 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 300 to 600 mg of the anti-IGF-1R antibody. In some embodiments, the therapeutically effective amount is 300 mg or 600 mg of the anti-IGF-1R antibody.

[00240] In some embodiments, the methods comprise administering an initial loading dose and at least one maintenance dose. In some embodiments, the initial loading dose is higher than the at least one maintenance dose. In some embodiments, the initial loading dose comprises administering multiple doses simultaneously or nearly simultaneously provided that the multiple doses cumulatively administers a therapeutically effective amount of the anti-IGF-1R antibody that is greater than the maintenance dose of the anti-IGF-1R antibody.

[00241] In some embodiments, the initial loading dose administers to the subject 400 mg to 800 mg, 500 mg to 800 mg, 600 mg to 800 mg, 700 mg to 800 mg, 500 mg to 800

mg, 500 mg to 700 mg, 500 mg to 600 mg, 600 mg to 800 mg, 600 mg to 700 mg, 550 mg to 650 mg, 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administers to the subject 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody. In some embodiments, the initial loading dose administers to the subject 600 mg.

[00242] In some embodiments, the maintenance, which can also be referred to as a subsequent dose administered after a loading dose is 100 mg to 500 mg, 100 mg to 400 mg, 100 mg to 300 mg, 100 mg to 200 mg, 100 mg to 400 mg, 200 mg to 500 mg, 200 mg to 400 mg, 200 mg to 300 mg, 300 mg to 500 mg, 300 mg to 400 mg, 250 mg to 350 mg, 275 mg to 325 mg, 285 mg to 315 mg, 100 mg, 200 mg, 275 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 325 mg, 400 mg, or 500 mg of the anti-IGF-1R antibody. In some embodiments, the maintenance dose is 300 mg.

[00243] In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 300 mg of an anti-IGF-1R antibody no more frequently than once every 2 weeks. In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 300 mg of an anti-IGF-1R antibody no more frequently than once every 4 weeks. In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 300 mg of an anti-IGF-1R antibody no more frequently than once every 8 weeks.

[00244] In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 600 mg of an anti-IGF-1R antibody as an initial loading dose and 300 mg of the IGF-1R antibody as a maintenance dose, wherein the maintenance dose is administered no more frequently than once every 2 weeks. In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 600 mg of an anti-IGF-1R antibody as an initial loading dose and 300 mg of the IGF-1R antibody as a maintenance dose, wherein the maintenance dose is administered no more frequently than once every 4 weeks. In some embodiments, a method comprises administering to the subject subcutaneously a pharmaceutical composition comprising 600 mg of an anti-IGF-1R antibody as an initial loading dose and 300 mg of the IGF-1R antibody as a maintenance dose, wherein the maintenance dose is administered no more frequently than once every 8 weeks.

[00245] In some embodiments, the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 10 ug/ml in the subject. In some embodiments, the serum concentration of at least 10 µg/ml is maintained for at 1 week (7 days), 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks.

[00246] In some embodiments, the pharmaceutical composition is administered every week, every 2 weeks, every 4 weeks, every 8 weeks, every 10 weeks, every 12 weeks, every 16 weeks, once a month, once every 2 months, once every 3 months, or once every 4 months. In some embodiments, the pharmaceutical composition is administered every 2 weeks, every 4 weeks, or every 8 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 2 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 3 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 4 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 4 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 4 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 5 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 6 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 7 weeks. In some embodiments, the pharmaceutical composition is administered no more frequently than once every 8 weeks. In some embodiments, the total number of doses administered to the subject is 1 to 10, 2, 3, 4, 5, 6, 7, 8, 9, 10 doses, 11 doses, or 12 doses. In some embodiments, the total number of doses administered to the subject is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 doses. In some embodiments, the doses include an initial loading dose as the first dose and a maintenance dose as the subsequent doses. In some embodiments, the initial loading dose comprises administering multiple doses simultaneously or nearly simultaneously provided that the multiple doses cumulatively administers a therapeutically effective amount of the anti-IGF-1R antibody that is greater than the maintenance dose of the anti-IGF-1R antibody.

[00247] In some embodiments, the therapeutically effective amount is administered every 4 weeks and produces a C_{avg} of 40 µg/ml to 70 µg/ml. In some embodiments, the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the C_{avg} is 45 µg/ml to 65 µg/ml, 50 µg/ml to 65 µg/ml, 55 µg/ml to 65 µg/ml, or 50 µg/ml to 60 µg/ml. In some embodiments, the C_{avg} is 55 µg/ml to 65 µg/ml.

[00248] In some embodiments, the therapeutically effective amount is administered every 4 weeks and produces a C_{min} of 40 to 60 $\mu\text{g/ml}$, 45 to 55 $\mu\text{g/ml}$, 50 to 60 $\mu\text{g/ml}$, 50 to 55 $\mu\text{g/ml}$. In some embodiments, the C_{min} is 50 to 55 $\mu\text{g/ml}$. In some embodiments, the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the C_{avg} is 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$ and the C_{min} is 50 to 55 $\mu\text{g/ml}$.

[00249] In some embodiments, the therapeutically effective amount is administered every 8 weeks and produces a C_{avg} of 20 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 20 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 45 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$. In some embodiments, the C_{avg} is 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$. In some embodiments, the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the therapeutically effective amount is administered every 8 weeks and produces a C_{min} of 10 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$ or 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$. In some embodiments, the C_{min} is 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$. In some embodiments, the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the C_{avg} is 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$ and the C_{min} of 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$.

[00250] In some embodiments, the therapeutically effective amount is administered every 2 weeks and produces a C_{avg} of 80 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$, 80 $\mu\text{g/ml}$ to 110 $\mu\text{g/ml}$, 80 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 110 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$, or 95 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$. In some embodiments, the C_{avg} is 95 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$. In some embodiments, the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the therapeutically effective amount is administered every 8 weeks and produces a C_{min} of 110 $\mu\text{g/ml}$ to 130 $\mu\text{g/ml}$, 120 $\mu\text{g/ml}$ to 130 $\mu\text{g/ml}$, 120 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$. In some embodiments, the C_{min} is 120 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$. In some embodiments, the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16. In some embodiments, the C_{avg} is 95 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$ and the C_{min} is 120 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$.

[00251] In some embodiments, the C_{min} is 17 $\mu\text{g/ml}$ with a Q8W dosing schedule, as measured after 16 weeks. In some embodiments, the C_{avg} is 38 $\mu\text{g/ml}$ with a Q8W dosing schedule, as measured after 16 weeks. In some embodiments, the C_{min} is 52 $\mu\text{g/ml}$ with a Q4W dosing schedule, as measured after 16 weeks. In some embodiments, the C_{avg} is 60

ug/ml with a Q4W dosing schedule, as measured after 16 weeks. In some embodiments, the C_{min} is 123 ug/ml with a Q2W dosing schedule, as measured after 16 weeks. In some embodiments, the C_{avg} is 98 ug/ml with a Q2W dosing schedule, as measured after 16 weeks.

[00252] In some embodiments, the C_{min} is 14 ug/ml with a Q8W dosing schedule, as measured after 24 weeks. In some embodiments, the C_{avg} is 35 ug/ml with a Q8W dosing schedule, as measured after 24 weeks. In some embodiments, the C_{min} is 54 ug/ml with a Q4W dosing schedule, as measured after 24 weeks. In some embodiments, the C_{avg} is 62 ug/ml with a Q4W dosing schedule, as measured after 24 weeks. In some embodiments, the C_{min} is 136 ug/ml with a Q2W dosing schedule, as measured after 24 weeks. In some embodiments, the C_{avg} is 116 ug/ml with a Q2W dosing schedule, as measured after 24 weeks.

[00253] In some embodiments, the subject that is administered the antibody subcutaneously does not produce detectable antidrug antibodies. In some embodiments, the antidrug antibodies are not detectable for at least 20, 24, or 28 weeks.

[00254] In some embodiments, the subject with thyroid eye disease does not have any significant adverse events after administration of the antibody. In some embodiments, the patient does not have any hearing impairment, ototoxic changes in audiometry, or hyperglycemic events after administration of the pharmaceutical composition. In some embodiments, the patient does not have any hearing impairment, ototoxic changes in audiometry, or hyperglycemic events caused by the administration of the pharmaceutical composition.

[00255] In some embodiments, after first dose of the antibody, the clinical activity score of the subject is reduced. In some embodiments, after two doses of the antibody, the clinical activity score of the subject is reduced.

Enumerated Embodiments

[00256] Embodiment 1. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a pharmaceutical composition comprising a therapeutically effective amount of an anti-IGF-1R antibody.

[00257] Embodiment 2. The method of embodiment 1, wherein the therapeutically effective amount is 200 g to 700 mg of the anti-IGF-1R antibody.

[00258] Embodiment 3. The method of embodiment 1 or 2, wherein the therapeutically effective amount is 300 to 600 mg of the anti-IGF-1R antibody.

- [00259] Embodiment 4. The method of any one of embodiments 1-3, wherein the therapeutically effective amount is 300 mg or 600 mg of the anti-IGF-1R antibody.
- [00260] Embodiment 5. The method of any one of embodiments 1-4, wherein the method comprises administering an initial loading dose and at least one maintenance dose.
- [00261] Embodiment 6. The method of embodiment 5, wherein the initial loading dose is higher than the at least one maintenance dose.
- [00262] Embodiment 7. The method of embodiment 5 or 6, wherein the initial loading dose comprises administering multiple doses simultaneously or nearly simultaneously provided that the multiple doses cumulatively administer a therapeutically effective amount of the anti-IGF-1R antibody that is greater than the maintenance dose of the anti-IGF-1R antibody.
- [00263] Embodiment 8. The method of any one of embodiments 5-7, wherein the initial loading dose administers to the subject 400 mg to 800 mg, 500 mg to 800 mg, 600 mg to 800 mg, 700 mg to 800 mg, 500 mg to 800 mg, 500 mg to 700 mg, 500 mg to 600 mg, 600 mg to 800 mg, 600 mg to 700 mg, 550 mg to 650 mg, 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody.
- [00264] Embodiment 9. The method of any one of embodiments 5-8, wherein the initial loading dose administers to the subject 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody.
- [00265] Embodiment 10. The method of any one of embodiments 5-9, wherein the initial loading dose administers to the subject 600 mg.
- [00266] Embodiment 11. The method of any one of embodiments 5-10, wherein the maintenance dose is 100 mg to 500 mg, 100 mg to 400 mg, 100 mg to 300 mg, 100 mg to 200 mg, 100 mg to 400 mg, 200 mg to 500 mg, 200 mg to 400 mg, 200 mg to 300 mg, 300 mg to 500 mg, 300 mg to 400 mg, 250 mg to 350 mg, 275 mg to 325 mg, 285 mg to 315 mg, 100 mg, 200 mg, 275 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 325 mg, 400 mg, or 500 mg of the anti-IGF-1R antibody.
- [00267] Embodiment 12. The method of any one of embodiments 5-11, wherein the maintenance dose is 300 mg.
- [00268] Embodiment 13. The method of any one of embodiments 1-12, wherein the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 10 µg/ml in the subject.

[00269] Embodiments 14. The method of embodiment 13, wherein the serum concentration of at least 10 µg/ml is maintained for at 1 week (7 days), 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks.

[00270] Embodiment 15. The method of any one of embodiments 1-14, wherein the pharmaceutical composition is administered every week, every 2 weeks, every 4 weeks, every 8 weeks, every 10 weeks, every 12 weeks, every 16 weeks, once a month, once every 2 months, once every 3 months, or once every 4 months.

[00271] Embodiment 16. The method of any one of embodiments 1-15, wherein the pharmaceutical composition is administered every 2 weeks, every 4 weeks, or every 8 weeks.

[00272] Embodiment 111. The method of any one of embodiments 1-15, wherein the pharmaceutical composition is administered every 4 weeks.

[00273] Embodiment 112. The method of any one of embodiments 1-15, wherein the pharmaceutical composition is administered every 8 weeks.

[00274] Embodiment 17. The method of any one of embodiments 1-16 and 111-112, wherein the total number of doses administered to the subject is 1 to 10, 2, 3, 4, 5, 6, 7, 8, 9, 10 doses, 11 doses, or 12 doses.

[00275] Embodiment 18. The method of embodiment 17, wherein the total number of doses administered to the subject is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 doses.

[00276] Embodiment 113. The method of embodiment 17, wherein the total number of doses administered to the subject is 3 doses.

[00277] Embodiment 114. The method of embodiment 17, wherein the total number of doses administered to the subject is 6 doses.

[00278] Embodiment 19. The method of any one of embodiments 17-18 and 113-114, wherein the doses include an initial loading dose as the first dose and a maintenance dose as the subsequent doses.

[00279] Embodiment 20. The method of embodiment 19, wherein the initial loading dose comprises administering multiple doses simultaneously or nearly simultaneously provided that the multiple doses cumulatively administer a therapeutically effective amount of the anti-IGF-1R antibody that is greater than the maintenance dose of the anti-IGF-1R antibody.

[00280] Embodiment 21. The method of any one of embodiments 1-20, wherein the therapeutically effective amount is administered every 4 weeks and produces a C_{avg} of 40 µg/ml to 70 µg/ml.

[00281] Embodiment 22. The method of embodiment 21, wherein the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.

[00282] Embodiment 23. The method of embodiment 21 or 22, wherein the C_{avg} is 45 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$ to 55 $\mu\text{g/ml}$, 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, or 50 $\mu\text{g/ml}$ to 60 $\mu\text{g/ml}$.

[00283] Embodiment 24. The method of any one of embodiments 21-23, wherein the C_{avg} is 50 $\mu\text{g/ml}$ to 55 $\mu\text{g/ml}$ or 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$.

[00284] Embodiment 25. The method of any one of embodiments 1-24, wherein the therapeutically effective amount is administered every 4 weeks and produces a C_{min} of 40 to 60 $\mu\text{g/ml}$, 45 to 55 $\mu\text{g/ml}$, 50 to 60 $\mu\text{g/ml}$, 50 to 55 $\mu\text{g/ml}$.

[00285] Embodiment 26. The method of embodiment 25, wherein the C_{min} of 50 to 55 $\mu\text{g/ml}$.

[00286] Embodiment 27. The method of embodiments 25 or 26, wherein the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.

[00287] Embodiment 28. The method of any one of embodiments 21-27, wherein the C_{avg} is 50 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$ and the C_{min} is 50 to 55 $\mu\text{g/ml}$.

[00288] Embodiment 29. The method of any one of embodiments 1-20, wherein the therapeutically effective amount is administered every 8 weeks and produces a C_{avg} of 20 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 20 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 45 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$.

[00289] Embodiment 30. The method of embodiment 29, wherein the C_{avg} is 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$.

[00290] Embodiment 31. The method of embodiments 29 or 30, wherein the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16.

[00291] Embodiment 32. The method of any one of embodiments 1-20 and 29-31, wherein the therapeutically effective amount is administered every 8 weeks and produces a C_{min} of 10 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$ or 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$.

[00292] Embodiment 33. The method of embodiment 32, wherein the C_{min} is 10 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$.

- [00293]** Embodiment 34. The method of embodiments 32 or 33, wherein the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.
- [00294]** Embodiment 35. The method of any one of embodiments 29-34, wherein the C_{avg} is 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$ and the C_{min} of 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$.
- [00295]** Embodiment 36. The method of any one of embodiments 1-20, wherein the therapeutically effective amount is administered every 2 weeks and produces a C_{avg} of 80 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$, 80 $\mu\text{g/ml}$ to 110 $\mu\text{g/ml}$, 80 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 110 $\mu\text{g/ml}$, 90 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$, or 95 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$.
- [00296]** Embodiment 37. The method of embodiment 36, wherein the C_{avg} is 95 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$.
- [00297]** Embodiment 38. The method of embodiments 37 or 38, wherein the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.
- [00298]** Embodiment 39. The method of any one of embodiments 1-20 and 36-38, wherein the therapeutically effective amount is administered every 2 weeks and produces a C_{min} of 110 $\mu\text{g/ml}$ to 140 $\mu\text{g/ml}$, 120 $\mu\text{g/ml}$ to 130 $\mu\text{g/ml}$, 130 $\mu\text{g/ml}$ to 140 $\mu\text{g/ml}$, 120 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$, 110 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$, or 120 $\mu\text{g/ml}$ to 140 $\mu\text{g/ml}$.
- [00299]** Embodiment 40. The method of embodiment 39, wherein the C_{min} is 120 $\mu\text{g/ml}$ to 140 $\mu\text{g/ml}$.
- [00300]** Embodiment 41. The method of embodiment 39 or 40, wherein the C_{min} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.
- [00301]** Embodiment 42. The method of any one of embodiments 36-41, wherein the C_{avg} is 95 $\mu\text{g/ml}$ to 120 $\mu\text{g/ml}$ and the C_{min} is 120 $\mu\text{g/ml}$ to 140 $\mu\text{g/ml}$.
- [00302]** Embodiment 43. The method of any one of embodiments 1-42, wherein the subject does not produce detectable antidrug antibodies or the level of antidrug antibodies is sufficiently low to not significantly impact the pK of the antibody or the antagonism of IGF-1R.
- [00303]** Embodiment 44. The method of embodiment 43, wherein the antidrug antibodies are not detectable for at least 20, 24, or 28 weeks.
- [00304]** Embodiment 45. The method of any one of embodiments 1-44, wherein the thyroid eye disease is acute thyroid eye disease.

[00305] Embodiment 46. The method of any one of embodiments 1-44, wherein the thyroid eye disease is chronic thyroid eye disease.

[00306] Embodiment 47. The method of embodiment 46, wherein the subject with chronic thyroid eye disease prior to administration of the first dose has had symptoms of thyroid eye disease for at least, or greater than, one year and has one or more of the following symptoms: lid retraction greater than 2 mm, exophthalmos (proptosis) of greater than or equal to 3 mm, Clinical Activity Score (CAS) from 0 to 7, and inconstant or constant diplopia.

[00307] Embodiment 48. The method of embodiment 47, wherein the exophthalmos is greater than or equal to 3 mm above the normal range for their race and gender.

[00308] Embodiment 49. The method of embodiment 47 or 48, wherein the subject has exophthalmos that is greater than or equal to 3 mm and a CAS from 0 to 7 greater than 2.

[00309] Embodiment 50. The method of any one of embodiments 46-49, wherein the subject, prior to administration of the pharmaceutical composition, had a CAS of greater than 0, 1, 2, 3, or 4, or 2 to 4.

[00310] Embodiment 51. The method of any one of embodiments 46-50, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 2, 3, 4, 5, 6, or 7 years, or 1 to 8 years, 1 to 7 years, 1 to 6 years, 1 to 5 years, 1 to 4 years, 1 to 3 years, 1 to 2 years, 2 to 8 years, 2 to 7 years, 2 to 6 years, 2 to 5 years, 2 to 4 years, 2 to 3 years, 3 to 8 years, 3 to 7 years, 3 to 5 years, 3 to 4 years, 4 to 8 years, 4 to 7 years, 4 to 6 years, 4 to 5 years, 5 to 8 years, 5 to 7 years, 5 to 6 years, 6 to 8 years, 6 to 7 years, or 7 to 8 years.

[00311] Embodiment 52. The method of any one of embodiments 46-51, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 63 months, 60 months, 48 months, 36 months, 24 months, or 12 months.

[00312] Embodiment 53. The method of any one of embodiments 45-42, wherein the patient does not have any hearing impairment, ototoxic changes in audiometry, or hyperglycemic events after administration of the pharmaceutical composition.

[00313] Embodiment 54. The method of any one of embodiments 46-53, wherein the patient does not have any hearing impairment, ototoxic changes in audiometry, or hyperglycemic events caused by the administration of the pharmaceutical composition.

[00314] Embodiment 55. The method of any one of embodiments 1-54, wherein the treated subject's proptosis is reduced by at least, or 1-4 mm.

- [00315] Embodiment 56. The method of embodiment 55, wherein the proptosis is reduced by at least, or 2-3 mm.
- [00316] Embodiment 57. The method of any one of embodiments 1-56, wherein the proptosis is reduced within 3 weeks of the first dose.
- [00317] Embodiment 58. The method of any one of embodiments 1-56, wherein the proptosis is reduced within 6 weeks of the first dose.
- [00318] Embodiment 59. The method of any one of embodiments 1-58, wherein the treated subject has reduced diplopia.
- [00319] Embodiment 60. The method of embodiment 59, wherein the diplopia is reduced within 3 weeks or 6 weeks of the first dose.
- [00320] Embodiment 61. The method of any one of embodiments 1-60, wherein the subject has an improvement in Clinical Activity Score (CAS) within 3 weeks or 6 weeks.
- [00321] Embodiment 62. The method of embodiment 61, wherein the CAS score has an improvement of at least -2, -3, or -4.
- [00322] Embodiment 63. The method of any one of embodiments 1-62, wherein the subject has a reduction in proptosis and an improvement in CAS score within 3 weeks or within 6 weeks of the first dose.
- [00323] Embodiment 64. The method of any one of embodiments 1-63, wherein the proptosis is reduced by 1 to 3 mm, 1 to 2 mm, 2 to 3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry or by MRI/CT.
- [00324] Embodiment 65. The method of any one of embodiments 1-64, wherein the proptosis is reduced by 2-3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry or by MRI/CT.
- [00325] Embodiment 66. The method of any one of embodiments 1-65, wherein after first dose of the antibody, the clinical activity score of the subject is reduced.
- [00326] Embodiment 67. The method of any one of embodiments 1-66, wherein after two doses of the antibody, the clinical activity score of the subject is reduced.
- [00327] Embodiment 68. The method of any one of embodiments 1-67, wherein the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, and a LCDR3 of SEQ ID NO: 3 and the heavy chain comprises a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.

[00328] Embodiment 69. The method of embodiment 68, wherein the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7.

[00329] Embodiment 70. The method of embodiment 68, wherein the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[00330] Embodiment 71. The method of embodiment 68, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[00331] Embodiment 72. The method of any one of embodiments 68-71, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9.

[00332] Embodiment 73. The method of any one of embodiments 68-71, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 10.

[00333] Embodiment 74. The method of any one of embodiments 68-71, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[00334] Embodiment 75. The method of any one of embodiments 68-71, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 10.

[00335] Embodiment 76. The method of any one of embodiments 68-71, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[00336] Embodiment 77. The method of any one of embodiments 1-67, wherein the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 12, a LCDR2 of SEQ ID NO: 13, and a LCDR3 of SEQ ID NO: 13 and the heavy chain comprises a HCDR1 of SEQ ID NO: 15, a HCDR2 of SEQ ID NO: 16 and a HCDR3 of SEQ ID NO: 17.

[00337] Embodiment 78. The method of embodiments 77, wherein the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18.

[00338] Embodiment 79. The method of embodiments 77, wherein the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

[00339] Embodiment 80. The method of embodiment 77, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 18 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19.

[00340] Embodiment 81. The method of any one of embodiments 77-80, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[00341] Embodiment 82. The method of any one of embodiments 77-80, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 21.

[00342] Embodiment 83. The method of any one of embodiments 77-80, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 21.

[00343] Embodiment 84. The method of any one of embodiments 1-67, wherein the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 22, a LCDR2 of SEQ ID NO: 23, and a LCDR3 of SEQ ID NO: 24 and the heavy chain comprises a HCDR1 of SEQ ID NO: 25, a HCDR2 of SEQ ID NO: 26 and a HCDR3 of SEQ ID NO: 27.

[00344] Embodiment 85. The method of embodiment 84, wherein the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28.

[00345] Embodiment 86. The method of embodiment 84, wherein the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29

[00346] Embodiment 87. The method of embodiment 84, wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 28 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 29.

[00347] Embodiment 88. The method of any one of embodiments 84-87, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30.

[00348] Embodiment 89. The method of any one of embodiments 84-87, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 31.

[00349] Embodiment 90. The method of any one of embodiments 84-87, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 30 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 31.

[00350] Embodiment 91. The method of embodiments 89 and 90, wherein the Fc region of the heavy chain comprises the mutations M252Y, S254T, and T256E, according to EU numbering.

[00351] Embodiment 92. The method of embodiments 89 and 90, wherein the Fc region of the heavy chain comprises the mutations M428L, and N434S, according to EU numbering.

[00352] Embodiment 93. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a pharmaceutical composition comprising a therapeutically effective amount of an anti-IGF-1R antibody, wherein the therapeutically effective amount is administered every 2 weeks, 4 weeks, or every 8 weeks in an amount of 300 mg, wherein the antibody comprises a light chain and a heavy chain, wherein the light chain comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, and a LCDR3 of SEQ ID NO: 3 and the heavy chain comprises a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.

[00353] Embodiment 94. The method of embodiment 93, wherein antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.

[00354] Embodiment 95. The method of embodiment 93 or 94, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[00355] Embodiment 96. The method of embodiments 93 or 94, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 10.

[00356] Embodiment 97. The method of any one of embodiments 93-96, wherein the method comprises administering an initial loading dose and at least one maintenance dose.

[00357] Embodiment 98. The method of embodiments 97, wherein the initial loading dose is higher than the at least one maintenance dose.

[00358] Embodiment 99. The method of embodiments 97 or 98, wherein the initial loading dose comprises administering multiple doses simultaneously or nearly simultaneously provided that the multiple doses cumulatively administer a therapeutically effective amount of the anti-IGF-1R antibody that is greater than the maintenance dose of the anti-IGF-1R antibody.

[00359] Embodiment 100. The method of any one of embodiments 97-99, wherein the loading dose is 300 mg to 800 mg, 300 to 600 mg, or 600 mg.

[00360] Embodiment 101. The method of any one of embodiments 93-100, wherein the therapeutically effective amount is administered every 4 weeks and produces a C_{avg} of 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$ and the C_{min} of 50 to 55 $\mu\text{g/ml}$.

[00361] Embodiment 102. The method of any one of embodiments 93-100, wherein the therapeutically effective amount is administered every 8 weeks and produces a C_{avg} of 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$ and a C_{min} of 15 $\mu\text{g/ml}$ to 20 $\mu\text{g/ml}$.

[00362] Embodiment 103. The method of any one of embodiments 93-100, wherein the therapeutically effective amount is administered every 2 weeks and produces a C_{avg} of 95 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$ and a C_{min} of 120 $\mu\text{g/ml}$ to 125 $\mu\text{g/ml}$.

[00363] Embodiment 104. The method of any one of embodiments 93-105, wherein the pharmaceutical composition comprises the antibody at a concentration of 25 mg/mL to 200 mg/mL, 100 mg/mL to 200 mg/mL, 125 mg/mL to 175 mg/mL, 140 mg/mL to 160 mg/mL, 145 mg/mL to 155 mg/mL.

[00364] Embodiment 105. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously an anti-IGF-1R antibody at a dose amount of 300 mg or 600 mg no more than once every 4 weeks, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

[00365] Embodiment 106. The method of embodiment 105, wherein the anti-IGF-1R antibody is administered at a dose amount of 300 mg.

[00366] Embodiment 107. The method of embodiment 105, wherein the anti-IGF-1R antibody is administered at a dose amount of 600 mg.

[00367] Embodiment 108. The method of any one of embodiments 105-107, wherein the anti-IGF-1R antibody is administered at once every 4 weeks, once every 6 weeks or once every 8 weeks.

[00368] Embodiment 109. The method of any one of embodiments 105-108, wherein the thyroid eye disease is acute thyroid eye disease.

[00369] Embodiment 110. The method of any one of embodiments 105-108, wherein the thyroid eye disease is chronic thyroid eye disease.

[00370] The subject matter is now described with reference to the following examples. These examples are provided for the purpose of illustration only and the claims should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teaching provided

herein. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially similar results.

EXAMPLES

Example 1: The Half Life of VRDN-003 Is Increased

[00371] A pharmaceutical composition comprising the antibody of VRDN-003 or VRDN-001 comprising the antibody at a concentration of 150 mg/mL was administered to healthy volunteers in an amount of 300 mg via subcutaneous injection. The concentration of each antibody in the serum of the healthy volunteers was measured. The half-life of VRDN-003 was found to be up to about 50 days with a bioavailability of about 59%. The PK profiles and half-lives are illustrated in **FIG. 1** comparing SC dosed VRDN-001 and VRDN-003 through 9 weeks

[00372] Additionally, the antibody was found to be well tolerated. No antidrug antibodies were detected through Day 29, 1 sample tested positive for ADA at Day 71 in the 300 mg SC group, and 5 samples tested positive for ADA at Day 120 (2 in 300 mg SC, and 3 in 600 mg SC). All titers were ≤ 90 and there was no correlation with ADA development and decreased PK exposure or PD response.

[00373] The amount of IGF-1 in the serum was also measured and it was found that a single dose of VRDN-003 increased IGF-1 comparable peak levels as VRDN-001, which also persisted longer in serum. This is illustrated in **FIG. 2**, where the onset of IGF-1 elevation correlates with the initiation of dosing, and resolves upon termination of dosing. Taken together, these data also demonstrates that to achieve IGF-1R saturation requires maintaining a serum concentration of at least 10 $\mu\text{g/mL}$.

[00374] The data and embodiments provided for herein demonstrated that VRDN-003 provides superior IGF-1 increases relative to VRDN-002 and also sustained for longer than VRDN-001. The half-life of subcutaneously administered VRDN-003 is also substantially greater than the half-life reported for lonigutamab (Gregory F. Keenan, et al. Presented as a Poster at the 49th North American Neuro Ophthalmology Society Annual Meeting, March 11 16, 2023, Orlando, FL).

EXAMPLE 2: Pharmacokinetic/Pharmacodynamic Modeling of VRDN-003 Demonstrates That The Antibody Can Be Administered Subcutaneously With Less Frequent Administration.

[00375] The relationship between the dosage of VRDN-003 and the serum concentrations of VRDN-003 observed in patients was further evaluated over time in a PK model as compared to IV doses administered of VRDN-001. Based on the modeling Q4W dosing of VRDN-003 SC is predicted to match or exceed the C_{min} of 3 mg/kg IV and 10 mg/kg IV exposure levels of VRDN-001. A C_{avg} is predicted to be about 60 $\mu\text{g/mL}$ and a C_{min} is predicted to be about 52 $\mu\text{g/mL}$, which is significantly higher than the threshold of the 10 $\mu\text{g/mL}$ predicted to be necessary for saturation of IGF-1R. These are illustrated in **FIG. 3A** and **FIG. 3B**, respectively.

[00376] Modeling was also performed based on a hypothetical 8 week dosing regimen (QW8) and it was predicted to exceed C_{min} and C_{avg} of 3 mg/kg IV administration of VRDN-001. The predicted C_{avg} and C_{min} was found to be about 38 $\mu\text{g/mL}$ and 17 $\mu\text{g/mL}$, respectively, as illustrated in **FIG. 4**.

[00377] Modeling was also performed based on a hypothetical 2 week dosing regimen (QW2) and it was predicted to match C_{avg} and beat C_{min} of 10 mg/kg IV administration of VRDN-001. The predicted C_{avg} and C_{min} was found to be about 98 $\mu\text{g/mL}$ and 123 $\mu\text{g/mL}$, respectively, as illustrated in **FIG. 5**.

[00378] Accordingly, the modeling of VRDN-003 predicts three infrequent subcutaneous dosing regimens that can be utilized. These different profiles can be summarized in illustrated in **FIG. 6**.

[00379] Further modeling was also done for a 24 week regimen and the modeling was found to have the following C_{avg} and C_{min} as indicated in the table below:

Dosing Schedule of VRDN-003 (300 mg subcutaneous)	C_{min} ($\mu\text{g/mL}$)	C_{avg} ($\mu\text{g/mL}$)
Q8W	14	35
Q4W	54	62
Q2W	136	116

Example 3: VRDN-002 Is Well Tolerated And Shows An Extended Half-Life Of About 30 To 40 Days In Healthy Volunteers.

[00380] A pharmaceutical composition comprising the antibody designated as VRDN-002 herein was administered intravenously or subcutaneously to volunteers in the amounts illustrated below. The half-life was determined to be about 30 to 40 days. The bioavailability was determined to be 45% by NCA and 58% by 2-compartment modeling. No subjects tested positive for antidrug antibodies following dosing with VRDN-002 IV or SC. The data regarding the administration of VRDN-002 is illustrated in **FIG. 7A** and **FIG. 7B**.

[00381] As the data demonstrates the antibodies provided herein can be administered subcutaneously with decreased frequency, which is a surprising and advantageous for patients being treated with thyroid eye disease and associated conditions such as those provided for herein.

[00382] All references cited herein are incorporated by reference to the same extent as if each individual publication, database entry (e.g. Genbank sequences or GeneID entries), patent application, or patent, was specifically and individually indicated to be incorporated by reference. This statement of incorporation by reference is intended by Applicants, pursuant to 37 C.F.R. §1.57(b)(1), to relate to each and every individual publication, database entry (e.g. Genbank sequences or GeneID entries), patent application, or patent, each of which is clearly identified in compliance with 37 C.F.R. §1.57(b)(2), even if such citation is not immediately adjacent to a dedicated statement of incorporation by reference. The inclusion of dedicated statements of incorporation by reference, if any, within the specification does not in any way weaken this general statement of incorporation by reference. Citation of the references herein is not intended as an admission that the reference is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

Example 4: A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Efficacy, Safety And Tolerability Study Of VRDN-003 In Participants With Active Thyroid Eye Disease (TED)

[00383] This example provides key information of Phase 3 study evaluating VRDN-003 in participants with active Thyroid Eye Disease (TED). This study will enroll adult participants with an onset of signs and symptoms of TED within 15 months of screening, commonly termed as “active” TED. Participants will receive 1 of 2 regimens of VRDN-003 administered subcutaneously (SC) or placebo. Participants who are non-responders, consent to

and are eligible may also receive additional SC treatment with VRDN-003 in the second portion of the study. Each participant will be in the study for approximately 56 weeks (including the screening period) and the study will involve safety evaluations as well as ocular assessments in both eyes. Participants who receive additional treatment with VRDN-003 in the second portion of the study will be in the study for approximately 74 weeks (including the screening period).

Study duration per participant

[00384] Each enrolled participant will be in the study for approximately 52 weeks following the first dose. Each enrolled participant who receives additional treatment with VRDN-003 in the second portion of the study will be in the study for approximately 70 weeks following the first dose.

Trial design

[00385] This is a randomized, double-masked, placebo-controlled, parallel-group study, where participants, site personnel (except pharmacy personnel preparing the injection), central imaging (MRI/CT) readers and sponsor will be masked to treatment. The study also includes an open-label portion for participants who consent and are eligible to receive additional SC treatment with VRDN-003.

[00386] Participants will receive one of the following dosing regimens:

- VRDN-003 Q4W: 300 mg VRDN-003 Q4W with 600 mg loading dose of VRDN-003
- VRDN-003 Q8W: 300 mg VRDN-003 Q8W with 600 mg loading dose of VRND-003
- Placebo: placebo Q4W

[00387] Participants in the VRDN-003 Q4W arm will receive a loading dose of 600 mg (given as 2 SC injections, each containing 300 mg VRDN-003 for a total of 600 mg) on Day 1 followed by 5 further single SC injections of 300 mg VRDN-003 Q4W on Weeks 4, 8, 12, 16 and 20.

[00388] Participants in the VRDN-003 Q8W arm will receive a loading dose of 600 mg (given as 2 SC injections, each containing 300 mg VRDN-003 for a total of 600 mg) on Day 1 followed by 2 further single SC injections of 300 mg VRDN-003 Q8W on Weeks 8 and 16 and 3 single SC injections of placebo on Weeks 4, 12 and 20 to maintain masking.

[00389] Participants in Placebo arm will receive 2 SC injections of placebo on Day 1 (to mimic the loading doses received by participants in the other 2 treatment arms on Day 1 to

maintain masking). This will be followed by 5 further single SC injections of placebo Q4W on Weeks 4, 8, 12, 16 and 20.

[00390] In order to maintain masking in all 3 arms, all participants will receive the same number of injections in the same dosing volume at applicable visits.

Key inclusion criteria

- Be an adult male or female participant, ≥ 18 to ≤ 75 years of age.
- Have a clinical diagnosis of TED with a CAS of ≥ 4 on the 7-item scale for the study eye.
- a). Have moderate to severe (i.e., has an appreciable impact on daily living) active TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender, and ≥ 17 mm at pre-dose baseline (Day 1) as measured by exophthalmometer and by MRI/CT, and at least one additional sign/symptom as described in the protocol; AND
- b.) Have at least one of the following: lid retraction of ≥ 2 mm, moderate or severe soft tissue involvement, inconstant or constant diplopia, spontaneous retrobulbar pain or pain on eye movement, swelling of the conjunctiva, eyelids or plica, or redness of the eyelids or plica in the study eye
- Have documented evidence of ocular symptoms or signs associated with active TED that began within 15 months prior to study screening.
- Not require immediate ophthalmological or orbital surgery in the study eye for any reason.
- Must agree to use highly effective contraception as specified in the protocol.
- Female TED participants must have a negative serum pregnancy test at screening.

Key exclusion criteria

- Have a decrease in CAS of ≥ 2 points in the study eye between screening assessment and Day 1.
- Have a decrease in proptosis of ≥ 2 mm in the study eye as measured by exophthalmometer between screening assessment and Day 1.
- Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future.
- Have corneal decompensation in the study eye unresponsive to medical management.
- Have had previous orbital irradiation or decompression surgery for TED to the study eye's orbit.

- Have abnormal baseline PTA audiometry (confirmed by repeated assessment) or history of significant ear pathology, relevant ear surgery, hearing impairment or hearing loss
- Have history or presence of inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease).
- Have received prior treatment with another anti-IGF-1R therapy
- Have received systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study drug (multivitamins containing selenium are permitted). Also exclusionary is periocular (including intraorbital) or intraocular administration of steroids within 3 months prior to the first dose of study drug or having received greater than 3 periocular or intraocular corticosteroid injections at any time. Steroids administered by local routes including eye drops, dermal, inhaled, nasal sprays and intra-articular steroids are permitted.
- Have received other immunosuppressive agents, including rituximab, tocilizumab, secukinumab, satralizumab or anti-FcRn's for any condition (including TED) or any other therapy for TED within 8 weeks prior to the first dose of study drug or have received intraorbital administration of other such immunosuppressive agents at any time. Note: artificial tears are permitted.
- Have received an investigational agent for any condition (including TED) within 8 weeks prior to the first dose of study drug.
- Have received radioactive iodine (RAI) treatment within 8 weeks prior to the first dose of study drug
- Be a pregnant or lactating woman
- Be an active alcoholic or illicit drug user or considered at high risk of relapse.
- Have a known hypersensitivity to any of the components of VRDN-003 or placebo formulations, or prior hypersensitivity to mAbs.
- Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2).
- Have a positive test for active hepatitis B or hepatitis C infection.
- Have previously participated in any study of VRDN-001 or VRDN-002 (also humanized mAbs directed to IGF-1R) or VRDN-003.

[00391] Eligibility for receiving open-label treatment with VRDN-003 will be determined after the Week 24 visit and require a participant to meet the following additional criteria.

Key Inclusion Criteria

- Have completed treatment per the randomization assignment and assessments required to determine proptosis responder status as measured by imaging (MRI/CT) at Week 24.
- Be a non-responder, as defined as either: (1) not achieving: a ≥ 2 mm reduction from baseline in proptosis in the study eye based on imaging (MRI/CT) at Week 24; or (2) a participant who achieved a ≥ 2 mm reduction from baseline in proptosis in the study eye based on imaging (MRI/CT) but had a corresponding increase of ≥ 2 mm from baseline in proptosis in the fellow eye based on imaging (MRI/CT) at Week 24
- If the participant has diabetes mellitus, have HbA1c of $<8.5\%$ at the Week 24 laboratory assessment.

Key Exclusion Criteria

- Have an abnormal PTA (confirmed by repeat assessment) at the Week 24 or Week 26 audiometry assessment or have had any AE of hearing impairment during the study that has not recovered or resolved.

Study Objectives

[00392] The primary objective of the study is to determine the efficacy of subcutaneously administered VRDN-003 using Q4W or Q8W regimen compared to placebo in participants with active TED. Secondary Objectives include evaluating the safety and tolerability, and the pharmacokinetics, pharmacodynamics and immunogenicity properties of VRDN-003 SC administered using a Q4W or Q8W regimen compared to placebo in participants with active TED. Exploratory Objectives will evaluate the safety, tolerability, and efficacy of VRDN-003 SC administered using a Q4W regimen in participants with active TED who previously received placebo or VRDN-003 and were deemed to be non-responders.

Efficacy Endpoints

[00393] The primary efficacy endpoint will be assessed as the proptosis responder rate in the study eye, or the overall responder rate in the study eye at Week 24. A participant will be classified as a proptosis responder if the participant achieves a ≥ 2 mm reduction from baseline in proptosis in the eye of interest (without a corresponding increase of ≥ 2 mm in the other eye). A participant will be classified as an overall responder if the participant achieves a ≥ 2 mm reduction from baseline in proptosis in the eye of interest (without a corresponding increase of ≥ 2 mm in the other eye) and a reduction in CAS ≥ 2 points from baseline in the same eye (without a corresponding increase of ≥ 2 points in the other eye).

[00394] Secondary endpoints will include (assessed at Week 24):

- Change from baseline in proptosis in the study eye;
- Proptosis Responder Rate in the study eye;
- Diplopia Responder Rate for participants with baseline Diplopia Score > 0 ;
- Diplopia Resolution Rate for participants with baseline Diplopia Score > 0 ;
- Overall Responder Rate in the study eye;
- Change from baseline in CAS in the study eye;
- Clinical Activity Responder Rate in the study eye; and
- Proportion of participants with a CAS score of 0 or 1 in the study eye.

[00395] A diplopia responder will be assessed as a participant with baseline Gorman Subjective Diplopia score > 0 who shows a reduction in Gorman Subjective Diplopia Score by ≥ 1 from baseline. A Clinical Activity responder will be assessed as a participant who shows a reduction in CAS ≥ 2 points from baseline in the eye of interest (without a corresponding increase of ≥ 2 points in the other eye). Diplopia resolution is defined as a reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia score > 0 .

[00396] Exploratory efficacy endpoints will include:

- Proptosis Responder Rate in the study and fellow eyes by visit;
- Durability of Proptosis Response in the study eye (in participants who were responders at Week 24) at Weeks 36 and 52;
- Overall Responder Rate in the study and fellow eyes by visit;
- Clinical Activity Responder Rate in the study and fellow eyes by visit;
- Diplopia Responder Rate by visit for those with baseline Diplopia Score > 0 ;
- Diplopia Resolution Rate by visit for those with baseline Diplopia Score > 0 ;
- Proportion of participants with a CAS score of 0 or 1 in the study and fellow eyes by visit for those with a baseline CAS > 0 ;
- Proportion of participants with absence of spontaneous retrobulbar pain in participants who had spontaneous retrobulbar pain at baseline;
- Proportion of participants with absence of eye motility induced pain in participants who had eye motility induced pain at baseline;
- Proportion of participants with absence of spontaneous retrobulbar pain or eye motility induced pain for participants who had either at baseline;
- Change from baseline in the following endpoints by visit:

- Proptosis in the study and fellow eyes ;
- CAS in the study and fellow eyes;
- Gorman Subjective Diplopia Score (for participants with baseline Diplopia Score > 0);
- Extraocular muscle volume in the study and fellow eyes;
- Orbital fat volume in the study and fellow eyes;
- Manual measurement of lid retraction in the study and fellow eyes;
- GO-QoL combined score;
- GO-QoL activity subscale;
- GO-QoL appearance subscale;
- EQ-5D-5L QoL questionnaire.

[00397] Primary and secondary endpoints that include proptosis will be based on imaging (MRI/CT) measurements. Within a given participant, the same imaging modality (MRI or CT) will be used throughout the study. The study eye will be the most proptotic eye based on imaging (MRI/CT) at the last assessment performed prior to the first administration of VRDN-003, and if both eyes are equally proptotic then the eye with the worse Visual Acuity (VA) will be selected. If proptosis and VA are equal in both eyes, then the right eye will be selected as the study eye.

[00398] Safety endpoints will assess the incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (SAEs). Pharmacokinetic (PK) endpoints will assess time of maximum serum concentration (T_{max}), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and terminal elimination half-life ($t_{1/2}$) of VRDN-003.

[00399] Pharmacodynamic and immunogenicity endpoints will assess IGF-1 and ADA levels at various time points pre- and post-injections.

[00400] In addition, evaluation of all the above endpoints, as applicable, will be conducted for participants who are non-responders at Week 24 in the first part of the study, who consent and are deemed eligible to receive an additional 20 weeks of open-label SC treatment with VRDN-003 (300 mg Q4W with 600 mg loading dose) in the second part of the study.

Example 5: A Phase 3, Randomized, Double-Masked, Placebo-Controlled, Efficacy, Safety And Tolerability Study Of VRDN-003 In Participants With Chronic Thyroid Eye Disease (TED)

[00401] This example provides key information of Phase 3 study evaluating VRDN-003 in participants with chronic Thyroid Eye Disease (TED). This study will enroll adult participants with an onset of signs and symptoms of TED more than 15 months prior to screening, commonly termed as “chronic” TED. Participants will receive 1 of 2 regimens of VRDN-003 administered subcutaneously (SC) or placebo. Participants who are non-responders, consent to and are eligible may also receive additional SC treatment with VRDN-003 in the second portion of the study. Each participant will be in the study for approximately 56 weeks (including the screening period) and the study will involve safety evaluations as well as ocular assessments in both eyes. Participants who receive additional treatment with VRDN-003 in the second portion of the study will be in the study for approximately 74 weeks (including the screening period).

Study duration per participant

[00402] Each enrolled participant will be in the study for approximately 52 weeks following the first dose. Each enrolled participant who receives additional treatment with VRDN-003 in the second portion of the study will be in the study for approximately 70 weeks following the first dose.

Trial design

[00403] This is a randomized, double-masked, placebo-controlled, parallel-group study, where participants, site personnel (except pharmacy personnel preparing the injection), central imaging (MRI/CT) readers and sponsor will be masked to treatment. The study also includes an open-label portion for participants who consent and are eligible to receive additional SC treatment with VRDN-003.

[00404] Participants will receive one of the following dosing regimens:

- VRDN-003 Q4W: 300 mg VRDN-003 Q4W with 600 mg loading dose of VRDN-003
- VRDN-003 Q8W: 300 mg VRDN-003 Q8W with 600 mg loading dose of VRND-003
- Placebo: placebo Q4W

[00405] Participants in the VRDN-003 Q4W arm will receive a loading dose of 600 mg (given as 2 SC injections, each containing 300 mg VRDN-003 for a total of 600 mg) on Day 1 followed by 5 further single SC injections of 300 mg VRDN-003 Q4W on Weeks 4, 8, 12, 16 and 20.

[00406] Participants in the VRDN-003 Q8W arm will receive a loading dose of 600 mg (given as 2 SC injections, each containing 300 mg VRDN-003 for a total of 600 mg) on Day 1 followed by 2 further single SC injections of 300 mg VRDN-003 Q8W on Weeks 8 and 16 and 3 single SC injections of placebo on Weeks 4, 12 and 20 to maintain masking.

[00407] Participants in Placebo arm will receive 2 SC injections of placebo on Day 1 (to mimic the loading doses received by participants in the other 2 treatment arms on Day 1 to maintain masking). This will be followed by 5 further single SC injections of placebo Q4W on Weeks 4, 8, 12, 16 and 20.

[00408] In order to maintain masking in all 3 arms, all participants will receive the same number of injections in the same dosing volume at applicable visits.

Key inclusion criteria

- Be an adult male or female participant, ≥ 18 to ≤ 75 years of age, with a maximum body weight of 125kg.
- Have a clinical diagnosis of TED with any CAS (0-7).
- Have moderate to severe (i.e., has an appreciable impact on daily living) chronic TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender, and ≥ 17 mm at pre-dose baseline (Day 1) as measured by exophthalmometer and by MRI/CT.
- Have documented evidence of ocular symptoms or signs associated with chronic TED that began > 15 months prior to study screening.
- Not require immediate ophthalmological or orbital surgery in the study eye for any reason.
- Must agree to use highly effective contraception as specified in the protocol.
- Female TED participants must have a negative serum pregnancy test at screening.

Key exclusion criteria

- Have a decrease in CAS of ≥ 2 points in the study eye between screening assessment and Day 1 for participants with a screening CAS ≥ 2 .
- Have a decrease in proptosis of ≥ 2 mm in the study eye as measured by exophthalmometer between screening assessment and Day 1.

- Have a compressive optic neuropathy of TED that is expected to require surgical decompression in the immediate future.
- Have corneal decompensation unresponsive to medical management.
- Have had previous orbital irradiation or decompression surgery for TED to the study eye's orbit.
- Have abnormal baseline PTA audiometry (confirmed by repeated assessment) or history of significant ear pathology, relevant ear surgery, hearing impairment or hearing loss.
- Have history or presence of inflammatory bowel disease (e.g., biopsy proven or clinical evidence of inflammatory bowel disease).
- Have received prior treatment with another anti-IGF-1R therapy.
- Have received systemic corticosteroids for any condition, including TED, or selenium within 2 weeks prior to the first dose of study drug (multivitamins containing selenium are permitted). Also exclusionary is periocular (including intraorbital) or intraocular administration of steroids within 3 months prior to the first dose of study drug or having received greater than 3 periocular or intraocular corticosteroid injections at any time. Steroids administered by local routes including eye drops, dermal, inhaled, nasal sprays and intra-articular steroids are permitted.
- Have received other immunosuppressive agents, including rituximab, tocilizumab, secukimumab, satralizumab or anti-FcRn's for any condition (including TED) or any other therapy for TED within 8 weeks prior to the first dose of study drug or have received intraorbital administration of other such immunosuppressive agents at any time. Note: artificial tears are permitted.
- Have received an investigational agent for any condition (including TED) within 8 weeks prior to the first dose of study drug.
- Have received radioactive iodine (RAI) treatment within 8 weeks prior to the first dose of study drug.
- Be a pregnant or lactating woman.
- Be an active alcoholic or illicit drug user or considered at high risk of relapse.

- Have a known hypersensitivity to any of the components of VRDN-003 or placebo formulations, or prior hypersensitivity to mAbs.
- Have a positive test for human immunodeficiency virus (HIV-1 and HIV-2).
- Have a positive test for active hepatitis B or hepatitis C infection.
- Have previously participated in any study of VRDN-001 or VRDN-002 (also humanized mAbs directed to IGF-1R) or VRDN-003.

[00409] Eligibility for receiving open-label treatment with VRDN-003 will be determined after the Week 24 visit and require a participant to meet the following additional criteria.

Key Inclusion Criteria

- Have completed treatment per the randomization assignment and assessments required to determine proptosis responder status as measured by imaging (MRI/CT) at Week 24.
- Be a non-responder, as defined as either: (1) not achieving: a ≥ 2 mm reduction from baseline in proptosis in the study eye based on imaging (MRI/CT) at Week 24; or (2) a participant who achieved a ≥ 2 mm reduction from baseline in proptosis in the study eye based on imaging (MRI/CT) but had a corresponding increase of ≥ 2 mm from baseline in proptosis in the fellow eye based on imaging (MRI/CT) at Week 24
- If the participant has diabetes mellitus, have HbA1c of $<8.5\%$ at the Week 24 laboratory assessment.

Key Exclusion Criteria

- Have an abnormal PTA (confirmed by repeat assessment) at the Week 24 or Week 26 audiometry assessment or have had any AE of hearing impairment during the study that has not recovered or resolved.

Study Objectives

[00410] The primary objective of the study is to determine the efficacy of subcutaneously administered VRDN-003 using Q4W or Q8W regimen compared to placebo in participants with chronic TED. Secondary Objectives include evaluating the safety and tolerability, and the pharmacokinetics, pharmacodynamics and immunogenicity properties of VRDN-003 SC administered using a Q4W or Q8W regimen compared to placebo in

participants with chronic TED. Exploratory Objectives will evaluate the safety, tolerability, and efficacy of VRDN-003 SC administered using a Q4W regimen in participants with chronic TED who previously received placebo or VRDN-003 and were deemed to be non-responders.

Efficacy Endpoints

[00411] The primary efficacy endpoint will be assessed as the proptosis responder rate in the study eye, or the overall responder rate in the study eye at Week 24. A participant will be classified as a proptosis responder if the participant achieves a ≥ 2 mm reduction from baseline in proptosis in the eye of interest (without a corresponding increase of ≥ 2 mm in the other eye). A participant will be classified as an overall responder if the participant achieves a ≥ 2 mm reduction from baseline in proptosis in the eye of interest (without a corresponding increase of ≥ 2 mm in the other eye) and a shows no worsening from baseline in CAS in the same eye (without a corresponding increase of ≥ 2 points in the other eye).

[00412] Secondary endpoints will include (assessed at Week 24):

- Change from baseline in proptosis in the study eye;
- Proptosis Responder Rate in the study eye;
- Overall Responder Rate in the study eye;
- Clinical Activity Responder Rate in the study eye;
- Diplopia Responder Rate for participants with baseline Diplopia Score > 0 ;
- Diplopia Resolution Rate for participants with baseline Diplopia Score > 0 ;

[00413] A diplopia responder will be assessed as a participant with baseline Gorman Subjective Diplopia score > 0 who shows a reduction in Gorman Subjective Diplopia Score by ≥ 1 from baseline. A Clinical Activity responder will be assessed as a participant who shows no worsening from baseline in CAS in the eye of interest (without a corresponding increase of ≥ 2 points in the other eye). Diplopia resolution is defined as a reduction in Gorman Subjective Diplopia Score to 0 from baseline for participants with baseline Gorman Subjective Diplopia score > 0 .

[00414] Exploratory efficacy endpoints will include:

- Proptosis Responder Rate in the study and fellow eyes by visit;
- Durability of Proptosis Response in the study eye (in participants who were responders at Week 24) at Weeks 36 and 52;
- Overall Responder Rate in the study and fellow eyes by visit;
- Clinical Activity Responder Rate in the study and fellow eyes by visit;

- Diplopia Responder Rate by visit for those with baseline Diplopia Score > 0;
- Diplopia Resolution Rate by visit for those with baseline Diplopia Score > 0;
- Proportion of participants with a CAS score of 0 or 1 in the study and fellow eyes by visit for those with a baseline CAS > 0;
- Proportion of participants with absence of spontaneous retrobulbar pain in participants who had spontaneous retrobulbar pain at baseline;
- Proportion of participants with absence of eye motility induced pain in participants who had eye motility induced pain at baseline;
- Proportion of participants with absence of spontaneous retrobulbar pain or eye motility induced pain for participants who had either at baseline;
- Change from baseline in the following endpoints by visit:
 - Proptosis in the study and fellow eyes ;
 - CAS in the study and fellow eyes;
 - Gorman Subjective Diplopia Score (for participants with baseline Diplopia Score > 0);
 - Extraocular muscle volume in the study and fellow eyes;
 - Orbital fat volume in the study and fellow eyes;
 - Manual measurement of lid retraction in the study and fellow eyes;
 - GO-QoL combined score;
 - GO-QoL activity subscale;
 - GO-QoL appearance subscale;
 - EQ-5D-5L QoL questionnaire.

[00415] Primary and secondary endpoints that include proptosis will be based on imaging (MRI/CT) measurements. Within a given participant, the same imaging modality (MRI or CT) will be used throughout the study. The study eye will be the most proptotic eye based on imaging (MRI/CT) at the last assessment performed prior to the first administration of VRDN-003, and if both eyes are equally proptotic then the eye with the worse Visual Acuity (VA) will be selected. If proptosis and VA are equal in both eyes, then the right eye will be selected as the study eye.

[00416] Safety endpoints will assess the incidence of treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (SAEs).

[00417] Pharmacokinetic (PK) endpoints will assess time of maximum serum concentration (T_{max}), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and terminal elimination half-life ($t_{1/2}$) of VRDN-003.

[00418] Pharmacodynamic and immunogenicity endpoints will assess IGF-1 and ADA levels at various time points pre- and post-injections.

[00419] In addition, evaluation of all the above endpoints, as applicable, will be conducted for participants who are non-responders at Week 24 in the first part of the study, who consent and are deemed eligible to receive an additional 20 weeks of open-label SC treatment with VRDN-003 (300 mg Q4W with 600 mg loading dose) in the second part of the study. The analyses of non-responders will be by the treatment regimen received in the main portion of the study. The endpoints will include timepoints/visits after the start of additional treatment.

[00420] The present embodiments are not to be limited in scope by the specific embodiments described herein. Indeed, various modifications in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the embodiments and any appended claims.

[00421] The present specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. Various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the present disclosure and any appended claims.

CLAIMS

1. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a therapeutically effective amount of an anti-IGF-1R antibody, wherein the therapeutically effective amount is 200 mg to 700 mg of the anti-IGF-1R antibody, and
wherein the antibody comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, a LCDR3 of SEQ ID NO: 3, a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.
2. The method of claim 1, wherein the therapeutically effective amount is 300 to 600 mg of the anti-IGF-1R antibody.
3. The method of claim 1 or 2, wherein the therapeutically effective amount is 300 mg or 600 mg of the anti-IGF-1R antibody.
4. The method of any one of claims 1-3, wherein the method comprises administering an initial loading dose and at least one maintenance dose.
5. The method of claim 4, wherein the initial loading dose is higher than the at least one maintenance dose.
6. The method of any one of claim 4-5, wherein the initial loading dose administered to the subject is 400 mg to 800 mg, 500 mg to 800 mg, 600 mg to 800 mg, 700 mg to 800 mg, 500 mg to 800 mg, 500 mg to 700 mg, 500 mg to 600 mg, 600 mg to 800 mg, 600 mg to 700 mg, 550 mg to 650 mg, 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody.
7. The method of any one of claims 4-6, wherein the initial loading dose administered to the subject is 575 mg to 625 mg, 585 mg to 615 mg, 595 mg to 605 mg, 590 mg, 595 mg, 600 mg, 605 mg, or 610 mg of the anti-IGF-1R antibody.
8. The method of any one of claims 4-7, wherein the initial loading dose administered to the subject is 600 mg.

9. The method of any one of claims 4-8, wherein the maintenance dose is 100 mg to 500 mg, 100 mg to 400 mg, 100 mg to 300 mg, 100 mg to 200 mg, 100 mg to 400 mg, 200 mg to 500 mg, 200 mg to 400 mg, 200 mg to 300 mg, 300 mg to 500 mg, 300 mg to 400 mg, 250 mg to 350 mg, 275 mg to 325 mg, 285 mg to 315 mg, 100 mg, 200 mg, 275 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 325 mg, 400 mg, or 500 mg of the anti-IGF-1R antibody.
10. The method of any one of claims 4-9, wherein the maintenance dose is 300 mg.
11. The method of any one of the preceding claims, wherein the therapeutically effective amount is an amount sufficient to produce a serum concentration of at least 10 µg/ml in the subject.
12. The method of claim 11, wherein the serum concentration of at least 10 µg/ml is maintained for at least 1 week (7 days), 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks.
13. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously a therapeutically effective amount of an anti-IGF-1R antibody, wherein the therapeutically effective amount comprises an initial dose of 600 mg and at least one maintenance dose of 300 mg, wherein the antibody comprises a LCDR1 of SEQ ID NO: 1, a LCDR2 of SEQ ID NO: 2, a LCDR3 of SEQ ID NO: 3, a HCDR1 of SEQ ID NO: 4, a HCDR2 of SEQ ID NO: 5 and a HCDR3 of SEQ ID NO: 6.
14. The method of any one of the preceding claims, wherein the anti-IGF-1R antibody is administered every week, every 2 weeks, every 4 weeks, every 8 weeks, every 10 weeks, every 12 weeks, every 16 weeks, once a month, once every 2 months, once every 3 months, or once every 4 months.
15. The method of any one of the preceding claims, wherein the anti-IGF-1R antibody is administered every 2 weeks, every 4 weeks, or every 8 weeks.

16. The method of any one of the preceding claims, wherein the anti-IGF-1R antibody is administered every 2 weeks, every 4 weeks, or every 8 weeks.
17. The method of any one of claims 1-15, wherein the anti-IGF-1R antibody is administered every 2 weeks, every 4 weeks, or every 8 weeks.
18. The method of any one of the preceding claims, wherein the total number of doses administered to the subject is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 doses.
19. The method of any one of the preceding claims, wherein the total number of doses administered to the subject is 3 doses.
20. The method of any one of claims 1-18, wherein the total number of doses administered to the subject is 6 doses.
21. The method of claim 18, wherein the doses include an initial loading dose as the first dose and a maintenance dose as the subsequent doses.
22. The method of any one of the preceding claims, wherein the therapeutically effective amount is administered every 4 weeks and produces a C_{avg} of 40 $\mu\text{g/ml}$ to 70 $\mu\text{g/ml}$.
23. The method of claim 22, wherein the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.
24. The method of claims 22 or 23, wherein the C_{avg} is 45 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, 50 $\mu\text{g/ml}$ to 55 $\mu\text{g/ml}$, 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$, or 50 $\mu\text{g/ml}$ to 60 $\mu\text{g/ml}$.
25. The method of any one of claims 22-24, wherein the C_{avg} is 50 $\mu\text{g/ml}$ to 55 $\mu\text{g/ml}$ or 55 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$.
26. The method of any one of the preceding claims, wherein the therapeutically effective amount is administered every 4 weeks and produces a C_{min} of 40 to 60 $\mu\text{g/ml}$, 45 to 55 $\mu\text{g/ml}$, 50 to 60 $\mu\text{g/ml}$, 50 to 55 $\mu\text{g/ml}$.

27. The method of claim 26, wherein the $C_{\min}$ of 50 to 55 $\mu\text{g/ml}$.
28. The method of claims 26 or 27, wherein the $C_{\min}$ is calculated for the period from the initial administration of the therapeutically effective amount through week 16 or week 24.
29. The method of any one of claims 22-28, wherein the C_{avg} is 50 $\mu\text{g/ml}$ to 65 $\mu\text{g/ml}$ and the $C_{\min}$ is 50 to 55 $\mu\text{g/ml}$.
30. The method of any one of claims 1-21, wherein the therapeutically effective amount is administered every 8 weeks and produces a C_{avg} of 20 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 20 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$, 30 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 45 $\mu\text{g/ml}$, 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$.
31. The method of claim 30, wherein the C_{avg} is 35 $\mu\text{g/ml}$ to 40 $\mu\text{g/ml}$.
32. The method of claims 30 or 31, wherein the C_{avg} is calculated for the period from the initial administration of the therapeutically effective amount through week 16.
33. The method of any one of the preceding claims, wherein the subject does not produce detectable antidrug antibodies or the level of antidrug antibodies is sufficiently low to not significantly impact the pK of the antibody or the antagonism of IGF-1R.
34. The method of claim 33, wherein the antidrug antibodies are not detectable for at least 20, 24, or 28 weeks.
35. The method of any one of the preceding claims, wherein the thyroid eye disease is active thyroid eye disease.
36. The method of any one of the preceding claims, wherein the thyroid eye disease is chronic thyroid eye disease.

37. The method of claim 36, wherein the subject with chronic thyroid eye disease prior to administration of the first dose has had

- (i) a clinical diagnosis of TED with any CAS (0-7).
- (ii) moderate to severe chronic TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender,
- (iii) proptosis of ≥ 17 mm in the study eye as measured by exophthalmometer or MRI/CT, or
- (iv) ocular symptoms or signs associated with chronic TED that began > 15 months prior to study screening.

38. The method of claim 35, wherein the subject with active thyroid eye disease prior to administration of the first dose has had

- (i) ocular symptoms or signs associated with active TED that began within 15 months prior to study screening,
- (ii) a clinical diagnosis of TED with a CAS of ≥ 3 ,
- (iii) moderate to severe active TED associated with proptosis as measured by exophthalmometer of ≥ 3 mm above normal values for race and gender,
- (iv) proptosis of ≥ 17 mm in the study eye as measured by exophthalmometer, or
- (v) one or more of the following symptoms: lid retraction of ≥ 2 mm, moderate or severe soft tissue involvement, inconstant or constant diplopia, spontaneous retrobulbar pain or pain on eye movement, swelling of the conjunctiva, eyelids or plica, or redness of the eyelids or plica in the study eye.

39. The method of claim 37 or 38, wherein the subject has proptosis greater than or equal to 3 mm above the normal range for their race and gender.

40. The method of claim 36, wherein the subject has a CAS from 0 to 7.

41. The method of claim 37, wherein the subject has a CAS greater than 4.

42. The method of any one of claims 37, and 39-41, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease more than 2, 3, 4, 5, 6, or 7 years, or 1 to 8 years, 1 to 7 years, 1 to 6 years, 1 to 5 years, 1 to 4 years, 1 to 3 years, 1 to 2 years, 2 to about 8 years, 2 to 7 years, 2 to 6 years, 2 to 5 years, 2 to 4 years, 2 to 3 years, 3 to 8 years, 3 to 7 years, 3 to 5 years, 3 to 4 years, 4 to 8 years, 4 to 7 years, 4 to 6 years, 4 to 5 years, 5 to 8 years, 5 to 7 years, 5 to 6 years, 6 to 8 years, 6 to 7 years, or 7 to 8 years.

43. The method of any one of claims 37, and 39-42, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease no more than 63 months, 60 months, 48 months, 36 months, 24 months, or 12 months.

44. The method of any one of claims 38-41, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 to 15 months, 2 to 13 months, 1 to 10 months, 1 to 12 months, 3 to 12 months, or 5 to 10 months.

45. The method of any one of claims 38-41, wherein the patient, prior to administration of the first dose, has had symptoms of thyroid eye disease for 1 month, for 2 months, for 3 months, for 4 months, for 5 months, for 6 months, for 7 months, for 8 months, for 9 months, for 10 months, for 11 months, for 12 months, for 13 months, for 14 months, or for 15 months.

46. The method of any one of the preceding claims, wherein the patient does not have any hearing impairment, ototoxic changes in audiometry, or hyperglycemic events after administration of the anti-IGF-1R antibody.

47. The method of any one of the preceding claims, wherein the treated subject's proptosis is reduced by at least, or 1-4 mm.

48. The method of claim 47, wherein the proptosis is reduced by at least, or 2-3 mm.

49. The method of any one of the preceding claims, wherein the proptosis is reduced within 3 weeks of the first dose.

50. The method of any one of the preceding claims, wherein the proptosis is reduced within 6 weeks of the first dose.
51. The method of any one of the preceding claims, wherein the treated subject has reduced diplopia.
52. The method of claim 51, wherein the diplopia is resolved in the treated subject.
53. The method of claim 51, wherein the diplopia is reduced within 3 weeks or 6 weeks of the first dose.
54. The method of any one of the preceding claims, wherein the subject has an improvement in Clinical Activity Score (CAS) within 3 weeks or 6 weeks.
55. The method of claim 54, wherein the CAS score has an improvement of at least -2, -3, or -4.
56. The method of any one of the claims 1-53, wherein the subject has no worsening of Clinical Activity Score (CAS) post treatment.
57. The method of any one of the preceding claims, wherein the subject has a reduction in proptosis and an improvement in CAS score within 3 weeks or within 6 weeks of the first dose.
58. The method of any one of the preceding claims, wherein the proptosis is reduced by 1 to 3 mm, 1 to 2 mm, 2 to 3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry or by MRI/CT.
59. The method of any one of the preceding claims, wherein the proptosis is reduced by 2-3 mm from baseline within 6 weeks of the first dose as measured by exophthalmometry or by MRI/CT.
60. The method of any one of the preceding claims, wherein after first dose of the antibody, the clinical activity score of the subject is reduced.

61. The method of any one of the preceding claims, wherein after two doses of the antibody, the clinical activity score of the subject is reduced.
62. The method of any one of the claims, wherein the patient with chronic TED exhibits fibrosis.
63. The method of claim 62, wherein the administration of the anti-IGF-1R antibody results in the treatment of fibrosis.
64. The method of claim 63, wherein fibrosis is reduced, alleviated, or reversed in the subject.
65. The method of any one of the preceding claims, wherein the light chain comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7.
66. The method of any one of the preceding claims, wherein the heavy chain comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.
67. The method of claim 65 or 66 wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8.
68. The method of any one of the preceding claims, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9.
69. The method of any one of the preceding claims, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 10.
70. The method of any one of the preceding claims, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.

71. The method of any one of claims 68-69, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 10.
72. The method of any one of claims 68 or 70, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.
73. The method of any one of the preceding claims, wherein the Fc region of the heavy chain comprises the mutations M252Y, S254T, and T256E, according to EU numbering.
74. The method of any one of claims 1-72, wherein the Fc region of the heavy chain comprises the mutations M428L, and N434S, according to EU numbering.
75. A method of treating thyroid eye disease in a subject, the method comprising administering to the subject subcutaneously an anti-IGF-1R antibody at a dose amount of 300 mg or 600 mg no more than once every 4 weeks, wherein the antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 9 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 11.
76. The method of claim 75, wherein the anti-IGF-1R antibody is administered at a dose amount of 300 mg.
77. The method of claim 75, wherein the anti-IGF-1R antibody is administered at a dose amount of 600 mg.
78. The method of any one of claims 75-77, wherein the anti-IGF-1R antibody is administered at once every 4 weeks, once every 6 weeks or once every 8 weeks.
79. The method of any one of claims 75-78, wherein the thyroid eye disease is active thyroid eye disease.

80. The method of any one of claims 75-78, wherein the thyroid eye disease is chronic thyroid eye disease.
81. The method of any of the claims, wherein the method further comprises administering magnesium to the subject.
82. The method of claim 81, wherein the magnesium is administered prior to, during, or after the administration of the anti-IGF-1R antibody.
83. The method of claim 82, wherein the magnesium is administered 1-2 days prior to subsequent administration of the anti-IGF-1R antibody.
84. The method of any one of claims 81-83, wherein the magnesium is administered at a dose of 200-600 mg.
85. The method of claim 84, wherein the magnesium is administered at 400 mg.
86. The method of any one of claims 81-85, wherein magnesium is administered orally.