

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-1beta, interferon-gamma, 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-IRalpha contains a ligand-binding domain while IGF-IRbeta is involved in signaling and contains 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

[0005a] In one aspect of the present disclosure, there is provided a composition for use in treating thyroid eye disease (TED) in a subject, the composition comprising an antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

[0005b] In another aspect of the present disclosure, there is provided an antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58; and

a Fc region comprising M252Y, S254T, and T256E mutations or M428L and N434S mutations.

[0005c] In a further aspect of the present disclosure, there is provided an antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 23, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 24, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 25, and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 26, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 27, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, and

a Fc region comprising M252Y, S254T, and T256E mutations or M428L and N434S mutations.

[0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody disclosed herein.

[0005e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition suitable for intravenous or subcutaneous administration comprising the antibody disclosed herein.

[0005f] In another aspect of the present disclosure, there is provided a pharmaceutical composition for use in treating thyroid eye disease (TED) in a subject comprising an antibody disclosed herein.

[0005g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition for use in treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) or a symptom thereof comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having the amino acid sequence of SEQ ID NO: 93 and a heavy chain having the amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005h] In another aspect of the present disclosure, there is provided a pharmaceutical composition for use in reducing proptosis in an eye in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005i] In a further aspect of the present disclosure, there is provided a pharmaceutical composition for use in reducing Clinical Activity Score (CAS) of thyroid-associated ophthalmopathy (TAO) in a subject comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005j] In another aspect of the present disclosure, there is provided a pharmaceutical composition for use in a) reducing proptosis by at least 2 mm and b) reducing the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005k] In a further aspect of the present disclosure, there is provided a composition for increasing the internalization of IGF-1R into a cell in a subject comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[00051] In another aspect of the present disclosure, there is provided a composition for inhibiting IGF-1 stimulated receptor phosphorylation on a cell in a subject comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005m] In a further aspect of the present disclosure, there is provided a use of a composition in the manufacture of a medicament for treating thyroid eye disease (TED) in a subject, the composition comprising an antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

[0005n] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for treating thyroid eye disease (TED) in a subject comprising an antibody disclosed herein.

[0005o] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) or a symptom thereof comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

- a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having the amino acid sequence of SEQ ID NO: 93 and a heavy chain having the amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005p] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for reducing proptosis in an eye in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of

SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005q] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for reducing Clinical Activity Score (CAS) of thyroid-associated ophthalmopathy (TAO) in a subject comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of

SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0005r] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for a) reducing proptosis by at least 2 mm and b) reducing the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of

SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody disclosed herein.

[0006] The ~~embodiment~~examples relate generally to IGF-1R antibodies, and antigen binding fragments 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~~disclosure 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 embodimentexamples, an antibody, or antigen binding fragment thereof, comprising a sequence as provided for herein is provided. In some embodimentexamples, the antibody comprises a VL sequence as set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 79, or 86; and a VH sequence as set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 80, or 83. In some embodimentexamples, the antibody comprises a LCDR sequence as set forth in SEQ ID NO: 17, 18, 19, 23, 24, 25, 29, 30, 31, 35, 36, 37, 41, 42, 43, 47, 48, 49, 53, 54, 55, 59, 60, 61, or 81, and a HCDR sequence as set forth in SEQ ID NO: 20, 21, 22, 26, 27, 28, 32, 33, 34, 38, 39, 40, 44, 45, 46, 50, 51, 52, 56, 57, 58, 62, 63, or 64; or any combination or variant thereof.

[0008] In some embodimentexamples, the antibody, or antigen binding fragment thereof, comprises a V_L peptide as set forth in SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 79, or 86, or any variant thereof. In some embodimentexamples, the antibody, or antigen binding fragment thereof, comprises a V_H peptide as set forth in SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 80, or 83, or any variant thereof.

[0009] In some embodimentexamples, the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 20, 26, 32, 38, 44, 50, or 56; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 21, 27, 33, 39, 45, 51, or 57; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 22, 28, 34, 40, 46, 52, or 58; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 17, 23, 29, 35, 41, 47, or 53; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 18, 24, 30, 36, 42, 48, or 54; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 19, 25, 31, 37, 43, 49, 55, or 81; or variants of any of the foregoing.

[0010] In some embodimentexamples, the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 20; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 21; and the heavy chain CDR3 sequence has the amino acid sequence of

SEQ ID NO: 22; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 17; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 18; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 19; or variants of any of the foregoing.

[0011] In some [embodimentexamples](#), the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 26; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 27; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 28; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 23; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 24; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 25; or variants of any of the foregoing.

[0012] In some [embodimentexamples](#), the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 32; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 33; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 34; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 29; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 30; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 31; or variants of any of the foregoing.

[0013] In some [embodimentexamples](#), the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 38; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 39; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 40; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 35; the light chain CDR2 sequence has the amino acid sequence of SEQ ID

NO: 36; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 37; or variants of any of the foregoing.

[0014] In some embodiment examples, the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 44; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 45; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 46; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 41; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 42; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 43; or variants of any of the foregoing.

[0015] In some embodiment examples, the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 50; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 51; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 52; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 47; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 48; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 49; or variants of any of the foregoing.

[0016] In some embodiment examples, the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 56; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 57; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 58; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 53; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 54; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 55; or variants of any of the foregoing.

[0017] In some [embodimentexamples](#), the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 62; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 63; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 64; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 59; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 60; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 61; or variants of any of the foregoing.

[0018] In some [embodimentexamples](#), the antibody or antibody fragment comprises: (i) a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 sequences, wherein the heavy chain CDR1 sequence has the amino acid sequence of SEQ ID NO: 38; the heavy chain CDR2 has the amino acid sequence of SEQ ID NO: 39; and the heavy chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 40; or variants of any of the foregoing; and (ii) a light chain variable region comprising light chain CDR1, CDR2, and CDR3 sequences, wherein the light chain CDR1 sequence has the amino acid sequence SEQ ID NO: 35; the light chain CDR2 sequence has the amino acid sequence of SEQ ID NO: 36; and the light chain CDR3 sequence has the amino acid sequence of SEQ ID NO: 81; or variants of any foregoing.

[0019] In some [embodimentexamples](#), the antibody comprises a V_L sequence as set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 79, or 86, or a variant thereof. In some [embodimentexamples](#), the antibody comprises a V_H sequence as set forth in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 80, or 83, or a variant thereof.

[0020] In some [embodimentexamples](#), the antibody comprises a sequence of SEQ ID NO: 65-72, 78, 82, or 85, or a variant thereof.

[0021] In some [embodimentexamples](#), the antibody comprises a light chain having the amino acid sequence of SEQ ID NO: 3 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 83. In some [embodimentexamples](#), the antibody comprising a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14.

[0022] In some [embodimentexamples](#), the antibody comprises a light chain having a an amino acid sequence of SEQ ID NO: 93 and a heavy chain amino acid sequence of SEQ ID NO: 92.

[0023] In some [embodimentexamples](#), the antibody comprises a light chain having a an amino acid sequence of SEQ ID NO: 93 and a heavy chain amino acid sequence of SEQ ID NO: 94.

[0024] In some [embodimentexamples](#), the antibody comprises a light chain having a an amino acid sequence of SEQ ID NO: 93 and a heavy chain amino acid sequence of SEQ ID NO: 95.

[0025] In some [embodimentexamples](#), the a variant of any antibodies provided herein are provided so long as the CDRs remain constant as compared to the parental (non-variant) sequence provided for herein.

[0026] In some [embodimentexamples](#), the antibody comprises a Fc region. In some [embodimentexample](#)s, the Fc region is as set forth in SEQ ID NO: 75-77, 84, 87, 88, 89, or 90. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 75. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 76. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 77. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 84. In some [embodimentexample](#)s, the Fc region is as set forth in SEQ ID NO: 87. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 88. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 89. In some [embodimentexamples](#), the Fc region is as set forth in SEQ ID NO: 90.

[0027] In some [embodimentexamples](#), pharmaceutical compositions comprising an antibody as provided for herein is provided.

[0028] In some [embodimentexamples](#), methods of treating or reducing the severity of, thyroid-associated ophthalmopathy (TAO), or a symptom thereof are provided, the methods comprising administering to a subject an antibody as provided for herein or a pharmaceutical composition comprising the same.

[0029] In some [embodimentexamples](#), methods of treating thyroid eye disease in a subject are provided, the methods comprising administering to a subject an antibody as provided for herein or a pharmaceutical composition comprising the same.

[0030] In some [embodimentexamples](#), methods of reducing Clinical Activity Score (CAS) of thyroid-associated ophthalmopathy (TAO) in a subject are provided, the methods comprising administering to a subject an antibody as provided for herein or a pharmaceutical composition comprising the same.

[0031] In some [embodimentexamples](#), methods of a) reducing proptosis by at least 2 mm and b) reducing the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO) are provided, the methods comprising administering to a subject an antibody as provided for herein or a pharmaceutical composition comprising the same.

[0032] In some [embodimentexamples](#), methods of treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) in a subject are provided, the methods comprising administering to a subject an antibody as provided for herein, or a pharmaceutical composition comprising the same, wherein 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).

[0033] In some [embodimentexamples](#), methods of improving the quality of life in a subject with thyroid-associated ophthalmopathy (TAO, also called Graves' Ophthalmopathy/Graves' Orbitopathy) are provided, the methods comprising administering to a subject an antibody as provided for herein, or a pharmaceutical composition comprising the same.

[0034] In some [embodimentexamples](#), methods of treating or reducing the severity of diplopia in a subject with thyroid-associated ophthalmopathy (TAO) are provided, the methods comprising administering to a subject an antibody as provided for herein, or a pharmaceutical composition comprising the same.

[0035] In some [embodimentexamples](#), methods of increasing the internalization of IGF-1R on a cell are provided, the methods comprising contacting the cell with an antibody as provided for herein or a pharmaceutical composition comprising the same.

[0036] In some [embodimentexamples](#), methods of inhibiting IGF-1 stimulated receptor phosphorylation on a cell are provided, the methods comprising contacting the cell with an as provided for herein, or a pharmaceutical composition comprising the same.

[0037] In some [embodimentexamples](#), methods of treating thyroid eye disease in a subject are provided, the methods comprising administering an as provided for herein, or a pharmaceutical composition comprising the same to the subject, wherein the antibody has a serum concentration in the subject of at least, or about, 70 µg/ml, 75 µg/ml, 80 µg/ml, 85 µg/ml, 90 µg/ml, 95 µg/ml, 100 µg/ml, or 105 µg/ml at least 1, 2, or 3 week after administration.

[0038] In some [embodimentexamples](#), methods of inhibiting IGF-1 induced receptor autophosphorylation in a cell by at least 95%, 96%, 97%, 98%, or 99% or by 100% are provided, the method comprising contacting the cell with an antibody as provided for herein, or a pharmaceutical composition comprising the same.

[0039] In some embodimentexamples, embodimentexamples are provided for any of the methods provided for herein, wherein the antibody, or an antigen binding fragment thereof, is administered in a pharmaceutical composition that additionally comprises a pharmaceutically acceptable diluent or excipient or carrier. In some embodimentexamples, the pharmaceutical composition further comprises one or more pharmaceutically active compounds for the treatment of TAO. In some embodimentexample, the pharmaceutical composition further comprises corticosteroids; rituximab or other anti-CD20 antibodies; tocilizumab or other anti-IL-6 antibodies; or selenium, infliximab or other anti-TNFalpha antibodies or a thyroid-stimulating hormone receptor (TSHR) inhibitor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] FIG. 1 illustrates the NHP (non-human primates) serum concentration of various antibodies and embodiments as provided for herein.

[0041] FIG. 2 illustrates various properties of antibodies as provided for herein.

[0042] FIG.3 illustrates various properties of antibodies as provided for herein.

[0043] FIG. 4 illustrates various properties of antibodies as provided for herein.

[0044] FIG. 5 illustrates various properties of antibodies as provided for herein.

[0045] FIG. 6 illustrates various properties of antibodies as provided for herein.

[0046] FIG. 7 illustrates various properties of antibodies as provided for herein.

[0047] FIG. 8 illustrates various properties of antibodies as provided for herein.

DETAILED DESCRIPTION

[0048] 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.

[0049] 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.

[0050] The terms "proptosis" and "exophthalmos" (also known as exophthalmos, 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

What is claimed is:

1. A ~~pharmaceutical~~ composition ~~comprising an antibody~~ for use in treating thyroid eye disease (TED) in a subject, the composition comprising an antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

2. The composition for use of claim 1, wherein the antibody comprises:

a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises the LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, the LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and the LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises the HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and the HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

3. The composition for use of claim 1, wherein the antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14.

~~2. The pharmaceutical composition of claim 1, wherein the antibody comprises a Fc region with M428L and N434S substitutions.~~

~~3. The pharmaceutical composition of claim 1, wherein the antibody comprises a Fc region with M428L, N434S, M252Y, S254T, and T256E substitutions.~~

~~4. The pharmaceutical composition of claim 1, wherein the antibody comprises a Fc region with M252Y, S254T, and T256E substitutions.~~

~~45. The ~~pharmaceutical~~ composition for use of claim 1, wherein the antibody comprises a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92.~~

~~6. The pharmaceutical composition of claim 1, wherein antibody comprises a light chain having a an amino acid sequence of SEQ ID NO: 93 and a heavy chain amino acid sequence of SEQ ID NO: 94.~~

~~7. The pharmaceutical composition of claim 1, wherein antibody comprises a light chain having a an amino acid sequence of SEQ ID NO: 93 and a heavy chain amino acid sequence of SEQ ID NO: 95.~~

5. An antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58; and

a Fc region comprising M252Y, S254T, and T256E mutations or M428L and N434S mutations.

6. The antibody of claim 5, wherein the antibody comprises:

a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises the LCDR1 comprising the

amino acid sequence of SEQ ID NO: 53, the LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and the LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises the HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, the HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and the HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

7. The antibody of claim 5, wherein the antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14.

8. The antibody of any one of claims 5-7, wherein the Fc region comprises M252Y, S254T, and T256E mutations.

9. The antibody of any one of claims 5-8, wherein the antibody comprises a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having amino acid sequence of SEQ ID NO: 94.

10. The antibody of any one of claims 5-7, wherein antibody comprises a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having amino acid sequence of SEQ ID NO: 95.

11. An antibody comprising:

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 23, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 24, and LCDR3 comprising the amino acid sequence of SEQ ID NO: 25, and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 26, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 27, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, and

a Fc region comprising M252Y, S254T, and T256E mutations or M428L and N434S mutations.

12. The antibody of claim 11, wherein the antibody comprises:

a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 98 and comprises the LCDR1 comprising the amino acid sequence of SEQ ID NO: 23, the LCDR2 comprising the amino acid sequence of SEQ ID NO: 24, and the LCDR3 comprising the amino acid sequence of SEQ ID NO: 25; and

a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 99 and comprises the HCDR1 comprising the amino acid sequence of SEQ ID NO: 26, the HCDR2 comprising the amino acid sequence of SEQ ID NO: 27, and the HCDR3 comprising the amino acid sequence of SEQ ID NO: 28.

13. The antibody of claim 11 or 12, wherein the antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 98 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 99.

14. The antibody of any one of claims 11-13, wherein the antibody comprises a light chain having the amino acid sequence of SEQ ID NO: 3 and a heavy chain having the amino acid sequence of SEQ ID NO: 83.

15. A pharmaceutical composition comprising the antibody of any one of claims 5-14.

168. A method of treating thyroid eye disease in a subject, the method comprising administering the pharmaceutical composition suitable for intravenous or subcutaneous administration comprising the antibody of any one of claims 5-141-7.

9. The method of claim 8, wherein the pharmaceutical composition is administered intravenously.

~~10. The method of claim 8, wherein the pharmaceutical composition is administered subcutaneously.~~

17. A pharmaceutical composition for use in treating thyroid eye disease (TED) in a subject comprising an antibody of any one of claims 5-14.

1844. A pharmaceutical composition for use in ~~A method of~~ treating or reducing the severity of, thyroid-associated ophthalmopathy (TAO)), or a symptom thereof, ~~the method~~ comprising an antibody, wherein the antibody comprises: ~~administering to a subject the pharmaceutical composition of any one of claims 1-7.~~

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having the amino acid sequence of SEQ ID NO: 93 and a heavy chain having the amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

1942. A pharmaceutical composition for use in~~A method of~~ reducing proptosis in an eye in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:), the method comprising administering to a subject the pharmaceutical composition of any one of claims 1-7.

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

~~13. A method of treating thyroid eye disease in a subject, the method comprising administering to a subject the pharmaceutical composition of any one of claims 2-4.~~

~~2014. A method of pharmaceutical composition for use in reducing Clinical Activity Score (CAS) of thyroid-associated ophthalmopathy (TAO) in a subject comprising an antibody, wherein the antibody comprises; the method comprising administering to a subject the pharmaceutical composition of any one of claims 1-7.~~

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a

- HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

2115. A ~~method of pharmaceutical composition for use in~~ a) reducing proptosis by at least 2 mm and b) reducing the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:); the method comprising administering to a subject the pharmaceutical composition of any one of claims 1-7.

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a

- HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

2216. The ~~method~~pharmaceutical composition for use of any of claims 18-2114-15, wherein proptosis is reduced by at least 2 mm;

~~17. The method of any of claims 11-15, wherein proptosis is reduced by at least 3 mm.~~

~~18. The method of any of claims 11-15, wherein proptosis is reduced by at least 4 mm.~~

~~19. The method of any of claims 11-15, wherein the clinical activity score (CAS) of the subject is reduced by at least 2 points; or severity of diplopia in the subject is reduced.~~

~~20. The method of any of claims 11-15, wherein the clinical activity score (CAS) of the subject is reduced to one (1).~~

~~21. The method of any of claims 11-15, wherein the clinical activity score (CAS) of the subject is reduced to zero (0).~~

~~22. A method of treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) in a subject comprising administering to a subject a pharmaceutical composition of any one of claims 1-7, wherein 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).

~~23. A method of improving the quality of life in a subject with thyroid-associated ophthalmopathy (TAO, also called Graves' Ophthalmopathy/Graves' Orbitopathy), the method comprising administering to a subject the pharmaceutical composition of any one of claims 1-7.~~

~~24. The method of claim 23, wherein 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.~~

~~25. The method of claim 23, wherein the treatment results in an improvement of greater than or equal to 8 points on the GO-QoL.~~

~~26. The method of claim 23, wherein the treatment results in an improvement on the Functioning subscale of the GO-QoL.~~

~~27. The method of claim 23, wherein the treatment results in an improvement on the Appearance subscale of the GO-QoL.~~

~~28. A method of treating or reducing the severity of diplopia in a subject with thyroid-associated ophthalmopathy (TAO), the method comprising administering to a subject the pharmaceutical composition of any one of claims 1-7.~~

~~29. The pharmaceutical composition for use of claim 22~~23~~method of claim 28~~, wherein the diplopia is constant diplopia;

~~30. The method of claim 28, wherein the diplopia is inconstant diplopia, or~~ ;

~~31. The method of claim 28, wherein the diplopia is intermittent diplopia.~~

~~32. The method of claim 28, wherein the improvement in or reduction in severity of diplopia is sustained at least 20 weeks after discontinuation of antibody administration.~~

~~33. The method of claim 28, wherein the improvement in or reduction in severity of diplopia is sustained at least 50 weeks after discontinuation of antibody administration.~~

~~34. The method of any one of claims 8-33, wherein said pharmaceutical composition is administered at a dosage of about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 20 mg/kg, about 20 mg/kg to about 30 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, or about 30 mg/kg of the antibody as a first dose.~~

~~35. The method of any one of claims 8-33, wherein said pharmaceutical composition is administered at a dosage of about 10 mg/kg to about 20 mg/kg of antibody as a first dose.~~

~~36. The method of any one of claims 8-33, wherein said pharmaceutical composition is administered at a dosage of about 1 mg/kg to about 10 mg/kg, about 2 mg/kg to about 5 mg/kg, or about 5 mg/kg to about 20 mg/kg of antibody in subsequent doses.~~

~~37. The method of any one of claims 8-33, wherein said pharmaceutical composition is administered in the following amounts: about 10 mg/kg antibody as a first dose; and about 20 mg/kg antibody in subsequent doses.~~

~~38. The method of claim 37, wherein said subsequent doses are administered every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, or every eight weeks for at least 21-52 weeks or longer.~~

2439. A ~~method of composition for~~ increasing the internalization of IGF-1R ~~into~~ a cell ~~in a~~ subject, ~~the method~~ comprising ~~an antibody, wherein the antibody comprises:~~ contacting the cell with the pharmaceutical composition of any one of claims 1-7.

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

25. A composition for inhibiting IGF-1 stimulated receptor phosphorylation on a cell in a subject comprising an antibody, wherein the antibody comprises:

a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;

d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or

e. the antibody of any one of claims 5-14.

~~40. The method of claim 39, wherein the contacting comprises administering to a subject the pharmaceutical composition of any one of claims 1-7.~~

~~2641.~~ The composition of claim 24 or 25~~method of claim 40~~, wherein the subject has or is at risk of thyroid eye disease (TED).

~~42.~~—A method of inhibiting IGF-1 stimulated receptor phosphorylation on a cell, the method comprising contacting the cell with the pharmaceutical composition of any one of claims 1-7.

~~43.~~—The method of claim 42, wherein the contacting comprises administering to a subject the pharmaceutical composition of any one of claims 1-7.

~~2744.~~ Use of a composition in the manufacture of a medicament for treating~~The method of claim 43, wherein the subject has or is at risk of~~ thyroid eye disease (TED) in a subject, the composition comprising an antibody comprising:-

a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

~~2845.~~ The use of claim 27~~method of any one of claims 42-44~~, wherein the antibody comprises:has an IC50 of less than, or equal to, about 0.2 nM, 0.15 nM, 0.10 nM, 0.09 nM.

a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence

~~46.~~—A method of SEQ ID NO: 13 and comprises the LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, the LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and the LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and

a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises the HCDR1 comprising the

amino acid sequence of SEQ ID NO: 56, the HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and the HCDR3 comprising the amino acid sequence of SEQ ID NO: 58.

29. The use of claim 27, wherein the antibody comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14.

30. The use of claim 27, wherein the antibody comprises a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92.

31. Use of a pharmaceutical composition in the manufacture of a medicament for treating thyroid eye disease (TED) in a subject, ~~the method~~ comprising an antibody administering the pharmaceutical composition of any one of claims ~~5-141-7 to the subject, wherein the antibody has a serum concentration in the subject of at least, or about, 10 µg/ml or 20 µg/ml or 50 µg/ml, 70 µg/ml, 75 µg/ml, 80 µg/ml, 85 µg/ml, 90 µg/ml, 95 µg/ml, 100 µg/ml, or 105 µg/ml at least 1, 2, or 3 weeks after administration.~~

32. Use of a pharmaceutical composition in the manufacture of a medicament for treating or reducing the severity of thyroid-associated ophthalmopathy (TAO) or a symptom thereof comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having the amino acid sequence of SEQ ID NO: 93 and a heavy chain having the amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

33. Use of a pharmaceutical composition in the manufacture of a medicament for reducing proptosis in an eye in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

34. Use of a pharmaceutical composition in the manufacture of a medicament for reducing Clinical Activity Score (CAS) of thyroid-associated ophthalmopathy (TAO) in a subject comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

35. Use of a pharmaceutical composition in the manufacture of a medicament for a) reducing proptosis by at least 2 mm and b) reducing the clinical activity score (CAS) in a subject with thyroid-associated ophthalmopathy (TAO) comprising an antibody, wherein the antibody comprises:

- a. a light chain variable region comprising a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of

SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;

- b. a light chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 13 and comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 53, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 54, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 55; and
a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 14 and comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 56, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 57, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 58;
- c. a light chain variable region having the amino acid sequence of SEQ ID NO: 13 and a heavy chain variable region having the amino acid sequence of SEQ ID NO: 14;
- d. a light chain having an amino acid sequence of SEQ ID NO: 93 and a heavy chain having an amino acid sequence of SEQ ID NO: 92; or
- e. the antibody of any one of claims 5-14.

36. The use of any of claims 32-35, wherein proptosis is reduced by at least 2 mm; clinical activity score (CAS) of the subject is reduced by at least 2 points; or severity of diplopia in the subject is reduced.

37. The use of claim 36, wherein the diplopia is constant diplopia, inconstant diplopia, or intermittent diplopia.

47. The method of claim 46, wherein the pharmaceutical composition is administered intravenously or subcutaneously.