METHODS OF TREATING GRAVES' OPHTHALMOPATHY USING ANTI-FCRN ANTIBODIES

The present disclosure claims the benefit of priority to U.S. Provisional Patent Application No. 62/756,472, filed November 6, 2018, which is incorporated herein by reference in its entirety.

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 30, 2019, is named 15193_0002-00304_SL.txt and is 34,216 bytes in size.

The present disclosure relates to therapeutic methods, uses, and compositions comprising an isolated anti-FcRn antibody or an antigen-binding fragment thereof that binds to neonatal Fc receptor (FcRn) to prevent, modulate, or treat Graves' ophthalmopathy. In certain aspects, the present disclosure provides methods of treating or preventing Graves' ophthalmopathy by administering an anti-FcRn antibody or an antigen-binding fragment thereof to a patient in need thereof. In certain aspects, the present disclosure provides pharmaceutical compositions for treating or preventing Graves' ophthalmopathy comprising an anti-FcRn antibody or an antigen-binding fragment thereof and at least one pharmaceutically acceptable carrier.

Antibodies are immunological proteins that bind to a specific antigen. In most animals, including humans and mice, antibodies are constructed from paired heavy and light polypeptide chains and each chain is made up of two distinct regions, referred to as the variable and constant regions. The heavy and light chain variable regions show significant sequence diversity between antibodies, and are responsible for binding to the target antigen. The constant regions show less sequence diversity, and are responsible for binding a number of natural proteins to elicit important biochemical events.

Under normal conditions, the average serum half-life of most IgG (i.e., IgG1, IgG2, and IgG4, excluding the IgG3 isotype) is about 21 days in humans (Morell et al., J. Clin. Invest.

49(4):673-80, 1970), which is a prolonged period relative to the serum half-life of other plasma proteins. With respect to this prolonged serum half-life of IgG, IgG that enters cells by endocytosis can strongly bind to neonatal Fc receptor (FcRn) in endosomes at a pH of 6.0 to avoid the degradative lysosomal pathway (FcRn, a type of Fc gamma receptor, is also referred to as FcRP, FcRB, or Brambell receptor). When the IgG-FcRn complex cycles to the plasma membrane, IgG dissociates rapidly from FcRn in the bloodstream at slightly basic pH (~7.4). By this receptor-mediated recycling mechanism, FcRn effectively rescues the IgG from degradation in lysosomes, thereby prolonging the half-life of IgG (Roopenian et al., J. Immunol. 170:3528, 2003).

FcRn was identified in the neonatal rat gut, where it functions to mediate the absorption of IgG from the mother's milk and facilitate IgG transport to the circulatory system. FcRn has also been isolated from human placenta, where it mediates absorption and transport of maternal IgG to the fetal circulation. In adults, FcRn is expressed in a number of tissues, including epithelial tissues of the lung, intestine, kidney, as well as nasal, vaginal, and biliary tree surfaces.

FcRn is a non-covalent heterodimer that typically resides in the endosomes of endothelial and epithelial cells. FcRn is a membrane bound receptor having three heavy chain alpha domains (α1, α2 and α3) and a single soluble light chain β2-microglobulin (β2m) domain. Structurally, it belongs to a family of major histocompatibility complex class 1 molecules that have β2m as a common light chain. The FcRn chain has a molecular weight of about 46 kDa and is composed of an ectodomain containing the α1, α2, and α3 heavy chain domains and a β2m light chain domain and having a single sugar chain, a single-pass transmembrane, and a relatively short cytoplasmic tail.

In order to study the contributions of FcRn to IgG homeostasis, mice have been engineered to “knockout” at least part of the genes encoding β2m and FcRn heavy chains so that the proteins are not expressed. In these mice, the serum half-life and concentrations of IgG were dramatically reduced, suggesting an FcRn-dependent mechanism for IgG homeostasis. It has also been

suggested that anti-human FcRn antibodies may be generated in these FcRn knockout mice, and that the antibodies may prevent binding of IgG to FcRn. The inhibition of IgG binding to FcRn negatively alters IgG serum half-life by preventing IgG recycling.

Graves' ophthalmopathy (also known as thyroid eye disease, thyroid associated orbitopathy, or Graves' orbitopathy) is an inflammatory disorder characterized by enlarged extraocular muscles and increased orbital fat, which in severe cases, can lead to diplopia and/or loss of vision (Bahn and Heufelder, N. Eng. J. Med. 329:1468-75, 1993). The disease passes through several phases. From onset, the first active/inflammatory phase involves worsening of signs and symptoms, which typically include swelling and redness of eyelids and conjunctiva, exophthalmos, double vision, and, in severe cases, corneal ulceration and decreased visual acuity (Wiersinga, Lancet Diabetes Endocrinol. 5:134-42, 2017). This first phase is generally followed by a gradual improvement in the inflammatory signs and symptoms until eventually no further changes occur. In the final inactive phase, the disease stabilizes but permanent abnormalities in both function and appearance may remain (Maheshwari and Weis, Indian J. Ophthalmol. 60:87-90, 2012).

Pathogenesis of Graves' ophthalmopathy is likely related to the activation of T lymphocytes (mostly CD4+) that invade the orbit and release cytokines, usually as a response to the presence of circulating auto-antibodies that bind to and stimulate the thyroid hormone receptor (TSHR). These cytokines are thought to act in a paracrine manner and induce the activation of fibroblasts due to an increase in the production of the hydrophilic glycosaminoglycans (GAGs) in the orbital tissue. The excessive secretion of GAGs together with the lymphocyte infiltration are believed to result in an osmotic pressure increase, significant tissue edema, and the clinical ophthalmopathy (Menconi et al., Autoimmun. Rev. 13:398–402, 2014; Marcocci and Marinò, Best Pract. Res. Clin. Endocrinol. Metab. 26:325-37, 2012).

In addition to pathogenic auto-antibodies directed at TSHR, it has also been suggested that auto-antibodies capable of activating insulin-like growth factor receptor (IGF-1R) signaling

may contribute to the pathogenesis of Graves' ophthalmopathy (Pritchard et al., J. Immunol. 170:6348-54, 2003). Studies investigating the IGF-1R signaling pathway have furthered the hypothesis that IGF-1R and TSHR form a functional receptor complex in thyroid and orbital tissue, and via the complex, IGF-1R might augment TSHR signaling (Tsui et al., J. Immunol. 181:4397-405, 2008). The exact nature of the interaction between IGF-1R and TSHR is not completely understood. Some data suggest that synergistic activation of hyaluronan secretion with simultaneous activation of TSHR and IGF-1R occurs, and that the effects of TSHR-stimulating antibodies are only partially blocked by an IGF-1R antagonist but can be completely blocked with a TSHR antagonist (Krieger et al., J. Clin. Endocrinol. Metab. 100:1071-7, 2015). Together, these data indicate that both TSHR and IGF-IR may play an important role in the pathogenesis of Graves' ophthalmopathy. However, despite recent progress in the understanding of its pathogenesis, Graves' ophthalmopathy remains a therapeutic challenge (Miguel et al., Saudi J. Ophthalmol. 32:139-45, 2018). Accordingly, an agent that can effectively block or antagonize the binding of anti-TSHR and/or anti-IGF-1R auto-antibodies to FcRn is a promising therapy for Graves' ophthalmopathy.

Graves' ophthalmopathy has been classified as an entity distinct from Graves' disease, which is an autoimmune disease characterized by hyperthyroidism with concomitant low levels of thyroid stimulating hormone. Only 25-50% of Graves' disease patients have clinically relevant Graves' ophthalmopathy. Likewise, although many patients with Graves' ophthalmopathy have a history of Graves' disease with hyperthyroidism, some are euthyroid with no such history or have hypothyroidism primarily caused by Hashimoto thyroiditis (Stan et al., Med. Clin. North Am. 96:311-28, 2012; Khoo et al., Thyroid 10:1093-100, 2000). Thus, Graves' ophthalmopathy may develop regardless of the presence of hyperthyroidism. The severity of the disease also does not correlate with thyroid function (Miguel et al., Saudi J. Ophthalmol. 32:139-45, 2018). Accordingly, it is understandable that treatments for Graves' disease and those targeted at the thyroid gland do not necessarily improve Graves' ophthalmopathy.

None of the therapies currently in use or under investigation for Graves' ophthalmopathy been shown to modify the course of the disease or reduce the need for surgical rehabilitation. Rather, current treatment options, such as glucocorticoids, nonsteroidal immunomodulators, and orbital radiotherapy (among others), often have burdensome side effects and demonstrate only limited efficacy during the active/inflammatory phase of the disease. Glucocorticoids, the most common form of treatment, are frequently associated with complications and severe adverse events, such as hepatotoxicity, cardiovascular or cerebrovascular events, autoimmune encephalitis, and liver test abnormalities. Likewise, non-specific nonsteroidal immunomodulators such as cyclosporine, azathioprine, and mycophenolate suppress the immune system as a whole, and therefore can have considerable off-target effects. The use of orbital radiotherapy is also limited due to the fear of toxicity and the risk of radiation-induced tumors. Thus, new and improved treatment options with both higher efficacy and lower toxicity are needed, particularly those showing higher efficacy during the active/inflammatory phase of the disease in order to prevent the occurrence of permanent changes.

Antibody-based therapies have been proposed to improve on and replace current treatment options (Wiersinga, Lancet Diabetes Endocrinol. 5:134-42, 2017). Rituximab, a chimeric monoclonal antibody against CD20, has been suggested as a possible replacement for intravenous corticosteroids, but has shown only limited efficacy in randomized controlled trials (Stan et al., J. Clin. Endocrinol. Metab. 100:432-41, 2015; Salvi et al., J. Clin. Endocrinol. Metab. 100:422-31, 2015). Teprotumumab, a fully human monoclonal antibody and a targeted inhibitor of IGF-1R, is also being investigated as a treatment for Graves' ophthalmopathy (NCT01868997; NCT03298867), and has received Breakthrough Therapy, Orphan Drug, and Fast Track designations from the U.S. Food and Drug Administration (FDA). However, teprotumumab is only expected to target and prevent IGF-1R signaling, whereas both IGF-IR and TSHR are believed to contribute to disease pathogenesis.

The present disclosure is based on the unexpected discovery that the use of an anti-FcRn

antibody or an antigen-binding fragment thereof that non-competitively inhibits the binding of IgG to FcRn is a promising therapeutic strategy to treat Graves' ophthalmopathy. The present disclosure, in various embodiments, provides a medicament or pharmaceutical composition comprising the antibody or antigen-binding fragment for effectively and fundamentally treating Graves' ophthalmopathy. Further, in various embodiments, the present disclosure provides a method of treating a patient suffering from Graves' ophthalmopathy by administering the antibody or antigen-binding fragment, or by administering a pharmaceutical composition comprising the antibody or antigen-binding fragment, to the patient.

In various embodiments, the present disclosure provides a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of an anti-FcRn antibody or an antigen-binding fragment thereof; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of an anti-FcRn antibody or an antigen-binding fragment thereof.

In various embodiments, the present disclosure provides an anti-FcRn antibody or an antigen-binding fragment thereof for use in a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, the method comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment, or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

In various embodiments, the present disclosure provides a use of an anti-FcRn antibody or an antigen-binding fragment thereof in a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

In various embodiments, the present disclosure provides a use of an anti-FcRn antibody or an antigen-binding fragment thereof in the manufacture of a medicament for treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

In various embodiments, the present disclosure provides a kit comprising an anti-FcRn antibody or an antigen-binding fragment thereof and instructions for use of the antibody or antigen-binding fragment in treating or preventing Graves' ophthalmopathy in a patient in need thereof.

In various embodiments, the present disclosure provides a pharmaceutical composition for use in treating or preventing Graves' ophthalmopathy in a patient in need thereof, the pharmaceutical composition comprising an anti-FcRn antibody or an antigen-binding fragment thereof, and at least one pharmaceutically acceptable carrier.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein (e.g., for treating or preventing Graves' ophthalmopathy), the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 27 (HCDR1), an amino acid sequence of SEQ ID No: 28 (HCDR2), and an amino acid sequence of SEQ ID No: 29 (HCDR3); and a light chain variable region comprising an amino acid sequence of SEQ ID No: 30 (LCDR1), an amino acid sequence of SEQ ID No: 31 (LCDR2), and an amino acid sequence of SEQ ID No: 32 (LCDR3). In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence of SEQ ID No: 16. In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 16. In various embodiments, the antibody or antigen-binding

fragment comprises a heavy chain amino acid sequence of SEQ ID No: 46; and a light chain amino acid sequence of SEQ ID No: 48.In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment is one of the antibodies or antigen-binding fragments disclosed in Intl. App. No. PCT/KR2015/004424 (Pub No. WO 2015/167293 A1), which is incorporated herein by reference.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment comprises:

CDR1 comprising one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 21, 24, 27, 30, 33, 36, 39, and 42;

CDR2 comprising one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 22, 25, 28, 31, 34, 37, 40, and 43; and

CDR3 comprising one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 23, 26, 29, 32, 35, 38, 41, and 44.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment comprises:

CDR1 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 21, 24, 27, 30, 33, 36, 39, and 42;

CDR2 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 22, 25, 28, 31, 34, 37, 40, and 43; and

CDR3 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 23, 26, 29, 32, 35, 38, 41, and 44.

In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 27 (HCDR1), an amino

acid sequence of SEQ ID No: 28 (HCDR2), and an amino acid sequence of SEQ ID No: 29 (HCDR3); and a light chain variable region comprising an amino acid sequence of SEQ ID No: 30 (LCDR1), an amino acid sequence of SEQ ID No: 31 (LCDR2), and an amino acid sequence of SEQ ID No: 32 (LCDR3).

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment comprises one or more heavy chain variable regions and one or more light chain variable regions, wherein the heavy chain variable regions and light chain variable regions comprise one or more amino acid sequences selected from the group consisting of amino acid sequences of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20.

In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence of SEQ ID No: 16.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment comprises one or more heavy chain variable regions and one or more light chain variable regions, wherein the heavy chain variable regions and light chain variable regions comprise an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of amino acid sequences of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20. In various embodiments, the heavy chain variable regions and light chain variable regions comprise an amino acid sequence that is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to one or more amino acid sequences selected from the group consisting of amino acid sequences of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20.

In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 16.

In various embodiments, the antibody or antigen-binding fragment binds to FcRn with a K_D (dissociation constant) of about 0.01 to about 2 nM at pH 6.0 or pH 7.4, as measured by, e.g., surface plasmon resonance (SPR). In various embodiments, the K_D is measured by surface plasmon resonance (e.g., human FcRn-immobilized surface plasmon resonance). In various embodiments, the K_D is measured by human FcRn-immobilized surface plasmon resonance.

In various embodiments, the antibody or antigen-binding fragment is any one of the antibodies or antigen-binding fragments disclosed or incorporated by reference herein.

In various embodiments of the therapeutic methods and uses disclosed herein, the antibody, antigen-binding fragment, or pharmaceutical composition is administered subcutaneously. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as one or more subcutaneous injections. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is contained in a syringe prior to administration. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as a single (i.e., one) subcutaneous injection. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as two consecutive subcutaneous injections. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as a fixed dose.

In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for 6 to 76 weeks, or any time period in between. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for at least 6 weeks, at least 12 weeks, at least 24 weeks, at least 26 weeks, at least 52 weeks, or at least 76 weeks. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for at least 76 weeks or more. In various embodiments, the antibody,

antigen-binding fragment, or pharmaceutical composition is administered once weekly for the entire active/inflammatory phase of Graves' ophthalmopathy, or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy generally comprises worsening of one or more signs and symptoms in a patient, e.g., swelling and redness of eyelids and conjunctiva, exophthalmos, double vision, corneal ulceration, and/or decreased visual acuity. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy has a duration of about 2 to about 3 years, and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for the entire phase or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy is less than about 2 years (e.g., about 1.5 years or less, about 1 year or less, etc.), and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for the entire phase or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy is more than about 3 years (e.g., about 3.5 years or more, about 4 years or more, etc.), and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for the entire phase or a portion thereof. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for only a portion of the active/inflammatory phase of Graves' ophthalmopathy. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly until sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence of one or more symptoms of Graves' ophthalmopathy.

In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks (bi-weekly). In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for 6 to 76 weeks, or any time period in between. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for at least 6 weeks, at least 12 weeks, at least 24 weeks, at least 26 weeks, at least 52 weeks, or at

least 76 weeks. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for at least 76 weeks or more. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for the entire active/inflammatory phase of Graves' ophthalmopathy, or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy has a duration of about 2 to about 3 years, and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for the entire phase or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy is less than about 2 years (e.g., about 1.5 years or less, about 1 year or less, etc.), and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for the entire phase or a portion thereof. In various embodiments, the active/inflammatory phase of Graves' ophthalmopathy is more than about 3 years (e.g., about 3.5 years or more, about 4 years or more, etc.), and the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for the entire phase or a portion thereof. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for only a portion of the active/inflammatory phase of Graves' ophthalmopathy. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks until sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence of one or more symptoms of Graves' ophthalmopathy.

In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is self-administered by the patient. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is self-administered by the patient at home. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered by a treating clinician. In various embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered alone, i.e., as a single agent. In various

embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered in combination with at least one additional therapeutic agent.

In various embodiments of the therapeutic methods and uses disclosed herein, the therapeutically effective amount of the antibody or antigen-binding fragment is about 200 to 300 mg, 300 to 400 mg, about 400 to 500 mg, or about 500 to 600 mg. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 200 to 300 mg, 300 to 400 mg, about 400 to 500 mg, or about 500 to 600 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 200 to 300 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 255 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 300 to 400 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 340 mg administered once weekly.

In various embodiments of the therapeutic methods and uses disclosed herein, the therapeutically effective amount of the antibody or antigen-binding fragment is about 550 to 650 mg, about 650 to 750 mg, or about 750 to 850 mg. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 550 to 650 mg, about 650 to 750 mg, or about 750 to 850 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 650 to 750 mg administered once weekly. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 680 mg administered once weekly.

In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is at least one dose of about 550 to 850 mg (e.g., about 680 mg), followed by at least one dose of about 300 to 600 mg (e.g., about 340 mg). In various embodiments, the at least one dose of about 550 to 850 mg is administered subcutaneously. In various embodiments, the

at least one dose of about 550 to 850 mg is administered as two consecutive subcutaneous injections. In various embodiments, the at least one dose of about 550 to 850 mg is administered intravenously. In various embodiments, the at least one dose of about 550 to 850 mg is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In various embodiments, the at least one dose of about 550 to 850 mg is about 3 doses. In various embodiments, the at least one dose of about 300 to 600 mg is administered subcutaneously. In various embodiments, the at least one dose of about 300 to 600 mg is administered as one subcutaneous injection. In various embodiments, the at least one dose of about 300 to 600 mg is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In various embodiments, the at least one dose of about 300 to 600 mg is about 3 doses. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is 3 doses of about 550 to 850 mg per dose, followed by 3 doses of about 300 to 600 mg per dose.

In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is at least one dose of about 680 mg, followed by at least one dose of about 340 mg. In various embodiments, the at least one dose of about 680 mg is administered subcutaneously. In various embodiments, the at least one dose of about 680 mg is administered as two consecutive subcutaneous injections. In various embodiments, the at least one dose of about 680 mg is administered intravenously. In various embodiments, the at least one dose of about 680 mg is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In various embodiments, the at least one dose of about 680 mg is about 3 doses. In various embodiments, the at least one dose of about 340 mg is administered subcutaneously. In various embodiments, the at least one dose of about 340 mg is administered as one subcutaneous injection. In various embodiments, the at least one dose of about 340 mg is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In various embodiments, the at least one dose of about 340 mg is about 3 doses. In various embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is 3 doses of 680 mg per dose, followed by 3 doses of

340 mg per dose.

In various embodiments of the therapeutic methods and uses disclosed herein, treatment with an anti-FcRn antibody or antigen-binding fragment reduces the level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in the patient and/or in a sample from the patient. In various embodiments, at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) comprises anti-TSHR IgG and/or anti-IGF-1R IgG. In various embodiments, treatment reduces the level of anti-TSHR IgG in the patient and/or in a sample from the patient by at least about 30%, about 40%, about 50%, about 60%, about 70%, or about 80%. In various embodiments, treatment reduces the level of anti-IGF-1R IgG in the patient and/or in a sample from the patient by at least about 30%, about 40%, about 50%, about 60%, about 70%, or about 80%. In various embodiments, treatment reduces the level of total serum IgG in the patient and/or in a sample from the patient. In various embodiments, treatment reduces the level of total serum IgG in the patient and/or in a sample from the patient by at least about 40%, about 50%, about 60%, about 70%, or about 80%.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the results of analyzing the expression of antibodies in CHO-S cells and analyzing HL161A, HL161B, HL161C, and HL161D antibody proteins, obtained by protein A purification, on SDS-PAGE gel under a reduced or non-reduced condition. Under a non-reduced condition, each of the HL161 antibodies had a whole human IgG1 type structure having a size of about 160 kDa, and under a reduced condition, the heavy chain had a size of about 55 kDa, and the light chain had a size of about 25 kDa. In **FIG. 1**, lane 1 represents a molecular weight (M.W.) marker, lane 2 represents 2 μg non-reduced (*NEM-treated) antibody, and lane 3 represents 2 μg reduced antibody.

FIG. 2A to **FIG. 2H** show the results of analysis performed using a surface plasmon resonance (SPR) system in order to determine the kinetic dissociation (K_D) of four antibodies

(HL161A, HL161B, HL161C, and HL161D) that bind to FcRn. The results in **FIG. 2A** to **FIG. 2H** were obtained by analyzing the interaction between human FcRn and the HL161A, HL161B, HL161C, or HL161D antibody at pH 6.0 and pH 7.4 using a Proteon GLC chip and a Proteon XPR36 (Bio-Rad) system.

FIG. 2A shows the results of analyzing the interaction between human FcRn and the HL161A antibody at pH 6.0.

FIG. 2B shows the results of analyzing the interaction between human FcRn and the HL161A antibody at pH 7.4.

FIG. 2C shows the results of analyzing the interaction between human FcRn and the HL161B antibody at pH 6.0.

FIG. 2D shows the results of analyzing the interaction between human FcRn and the HL161B antibody at pH 7.4.

FIG. 2E shows the results of analyzing the interaction between human FcRn and the HL161C antibody at pH 6.0.

FIG. 2F shows the results of analyzing the interaction between human FcRn and the HL161C antibody at pH 7.4.

FIG. 2G shows the results of analyzing the interaction between human FcRn and the HL161D antibody at pH 6.0.

FIG. 2H shows the results of analyzing the interaction between human FcRn and the HL161D antibody at pH 7.4.

FIG. 3 shows the ability of two selected antibodies to bind to the cell surface, and shows the results obtained by treating human FcRn-overexpressing HEK293 cells with selected HL161A and HL161B antibodies binding to human FcRn present on the cell surface and analyzing the antibodies binding to the cell surface at pH 6.0 and pH 7.4. The binding of each of the HL161A and HL161B antibodies to human FcRn was expressed as an MFI value obtained by performing fluorescent activated cell sorter (FACS) using Alexa488-labeled anti-human goat antibody after

treating cells with each antibody at varying pHs.

FIG. 4 shows the results of analyzing the ability to block the binding of human IgG to human FcRn-expressing cells at pH 6.0, and shows the results of observing whether two selected antibodies binding to cell surface human FcRn can block the binding of human IgG to human FcRn, at the cell level. A profile of the ability to block the binding of Alexa488-labeled human IgG to human FcRn was obtained by diluting each of HL161A and HL161B antibodies, confirmed to bind to human FcRn-overexpressing HEK293 cells, serially 4-fold from 200 nM.

FIG. 5A and **FIG. 5B** show the results of analyzing the effects of HL161A and HL161B antibodies, selected from human FcRn-expressing transgenic mouse Tg32 (hFcRn+/+, hβ2m+/+, mFcRn-/-, mβ2m-/-), on the catabolism of hIgG1. At 0 hour, 5 mg/kg of biotin-hIgG and 495 mg/kg of human IgG were intraperitoneally administered to saturate IgG *in vivo*. Regarding drug administration, at 24, 48, 72, and 96 hours after administration of biotin-IgG, IgG1, HL161A, HL161B, or PBS was injected intraperitoneally at doses of 5, 10 and 20 mg/kg once a day. Sample collection was performed at 24, 48, 72, 96, 120, and 168 hours after administration of biotin-IgG. At 24, 48, 72, and 96 hours, blood was collected before drug administration, and the remaining amount of biotin-IgG was analyzed by an ELISA method. The results were expressed as the ratio of the remaining amount at each time point to 100% for the remaining amount in the blood sample collected at 24 hours.

FIG. 6A to **FIG. 6C** show the results of analyzing the change in blood level of monkey IgG caused by administration of two antibodies (HL161A and HL161B) to cynomolgus monkeys having a sequence homology of 96% to human FcRn. Each of HL161A and HL161B antibodies was administered intravenously to cynomolgus monkeys at doses of 5 mg/kg and 20 mg/kg once a day.

FIG. 6A shows the serum IgG-reducing effects of HL161A and HL161B antibodies at varying antibody concentrations.

FIG. 6B shows the serum IgG-reducing effects of HL161A and HL161B antibodies

(concentration: (5 mg/kg) in monkey individuals).

FIG. 6C shows the serum IgG-reducing effects of HL161A and HL161B antibodies (concentration: (20 mg/kg) in monkey individuals).

FIG. 7A and **FIG. 7B** show the results of analyzing the pharmacokinetic profiles of HL161A and HL161B in an experiment performed using cynomolgus monkeys.

FIG. 8A to **FIG. 8C** show the results of analyzing the changes in blood levels of monkey IgM, IgA, and albumin caused by administration of HL161A and HL161B antibodies in an experiment performed using cynomolgus monkeys.

FIG. 8A shows a change in the serum IgM level of monkeys.

FIG. 8B shows a change in the serum IgA level of monkeys.

FIG. 8C shows a change in the serum albumin level of monkeys.

FIG. 9 shows the study design of an open-label, add-on-to-standard-of-care study to assess the safety and tolerability of RVT-1401 (HL161BKN) in patients with moderate to severe active Graves' ophthalmopathy. Patients diagnosed with moderate to severe active Graves' ophthalmopathy with evidence of anti-TSHR-IgG are treated with once weekly subcutaneous doses of RVT-1401 (680 mg for 2 weeks, followed by 340 mg for 4 weeks).

FIG. 10 shows the study design of a randomized, double-blind, placebo-controlled, add-on-to-standard-of-care study to assess the efficacy and safety of RVT-1401 (HL161BKN) in patients with moderate to severe active Graves' ophthalmopathy. Patients diagnosed with moderate to severe active Graves' ophthalmopathy with evidence of anti-TSHR-IgG are randomized (2:2:1:2) and treated with once weekly subcutaneous doses of RVT-1401 (680 mg, 340 mg, or 255 mg) for 12 weeks, or placebo for 12 weeks.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

In order that the disclosure may be more readily understood, certain terms are defined throughout the detailed description. Unless defined otherwise herein, all scientific and technical terms used in connection with the present disclosure have the same meaning as commonly understood by those of ordinary skill in the art. All references cited herein are also incorporated by reference in their entirety. To the extent a cited reference conflicts with the disclosure herein, the specification shall control.

As used herein, the singular forms of a word also include the plural form, unless the context clearly dictates otherwise; as examples, the terms "a," "an," and "the" are understood to be singular or plural. By way of example, "an element" means one or more element. The term "or" shall mean "and/or" unless the specific context indicates otherwise. All ranges include the endpoints and all points in between unless the specific context indicates otherwise.

In some embodiments, the present disclosure is directed to a method of treating or preventing Graves' ophthalmopathy by administering an anti-FcRn antibody or an antigen-binding fragment thereof, or by administering a pharmaceutical composition comprising an anti-FcRn antibody or an antigen-binding fragment thereof and at least one pharmaceutically acceptable carrier, to a patient in need of treatment. In some embodiments, the present disclosure is directed to a use of an anti-FcRn antibody or an antigen-binding fragment thereof in a method of treating or preventing Graves' ophthalmopathy and/or in the manufacture of a medicament for treating or preventing Graves' ophthalmopathy, by administering the anti-FcRn antibody or antigen-binding fragment, or by administering a pharmaceutical composition comprising the anti-FcRn antibody or antigen-binding fragment and at least one pharmaceutically acceptable carrier, to a patient in need of treatment. Pharmaceutical compositions comprising an anti-FcRn antibody or an antigen-binding fragment thereof and at least one pharmaceutically acceptable carrier are also disclosed, and are useful in the therapeutic methods and uses described herein.

As used herein, the term "treat" and its cognates refer to an amelioration of a disease, disorder, or condition (e.g., Graves' ophthalmopathy), or at least one discernible symptom thereof (e.g., any one or more of the signs and symptoms described herein). The term "treat" encompasses but is not limited to complete treatment or complete amelioration of one or more symptoms of Graves' ophthalmopathy. In some embodiments, "treat" refers to at least partial amelioration of at least one measurable physical parameter, not necessarily discernible by the patient, e.g., a reduction in the level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG, e.g., anti-TSHR IgG and/or anti-IGF-1R IgG) and/or the level of total serum IgG. In some embodiments, "treat" refers to inhibiting the progression of a disease, disorder, or condition, either physically (e.g., stabilization of a discernible symptom), physiologically (e.g., stabilization of a physical parameter), or both. In some embodiments, "treat" refers to slowing the progression or reversing the progression of a disease, disorder, or condition. As used herein, "treat" and its cognates also encompass delaying the onset or reducing the risk of acquiring a given disease, disorder, or condition. The antibodies, antigen-binding fragments, and pharmaceutical compositions disclosed herein can also be used in the prevention or prophylaxis of a disease, disorder, or condition. For instance, a prophylactic method can comprise administering to a subject at risk of developing the disease, disorder, or condition (e.g., Graves' ophthalmopathy) an antibody, antigen-binding fragment, or pharmaceutical composition disclosed herein to prevent or reduce the odds developing the disease, disorder, or condition, or at least one discernible symptom thereof. In some embodiments, the disease, disorder, or condition is Graves' ophthalmopathy.

The terms "subject" and "patient" are used interchangeably herein to refer to any human or non-human animal. Non-human animals include all vertebrates (e.g., mammals and non-mammals) such as any mammal. Non-limiting examples of mammals include humans, mice, rats, rabbits, dogs, monkeys, and pigs. In various embodiments, the subject is a human. In various embodiments, the subject is a human having or suspected of having Graves' ophthalmopathy.

As used herein, the terms "Graves' ophthalmopathy," "Graves' orbitopathy," "thyroid associated orbitopathy," and "thyroid eye disease" are used interchangeably to refer to the autoimmune inflammation of extraocular muscles and orbital fat or connective tissue. Signs and symptoms of Graves' ophthalmopathy generally involve but are not limited to swollen extraocular muscles and expansion of orbital fat and connective tissue, and include swelling and redness of eyelids and conjunctiva, exophthalmos, double vision, and, in severe cases, corneal ulceration and decreased visual acuity. The degree of severity of Graves' ophthalmopathy can be classified as mild, moderate to severe, or sight-threatening, following quantitative assessment of lid aperture width, proptosis measurement, diplopia score (1 = intermittent [i.e., when tired or on awakening]; 2 = inconstant [i.e., only at extremes of gaze]; 3 = constant), degrees of abduction in eye muscle movement, examination of the cornea for evidence of exposure keratitis or ulceration, and assessment of optic nerve function (Bartalena et al., Thyroid 18:333-46, 2008). The activity of Graves' ophthalmopathy can be graded using a clinical activity score (CAS) that ranges from 0 to 7 or from 0 to 10 and predicts response to anti-inflammatory therapies (Mourits et al., Br. J. Ophthalmol. 73:639-44, 1989; Mourits et al., Clin. Endocrinol. 47:9-14, 1997). Clinical assessment of Graves' ophthalmopathy may also include evaluation of the impact of the disease on the patient's quality of life (QOL). QOL has been shown to be impaired in Graves' ophthalmopathy, with both physical and mental health being adversely affected. Generally, patients have poorer self-image, more sleep disturbance, and more impaired social and work functioning than controls (Yeatts, Trans. Am. Ophthalmol. Soc. 103:368-411, 2005). Several QOL questionnaires have been developed and validated for use in patients with Graves' ophthalmopathy (Terwee et al., Br. J. Ophthalmol. 82:773-9, 1998; Terwee et al., Clin. Endocrinol. 54:391-8, 2001).

In some embodiments, a patient in need of treatment for Graves' ophthalmopathy has (1) CAS $\geq$ 4 for more severely affected eye; (2) moderate to severe active disease; (3) onset of active eye disease within 9 months; and/or (4) detectable auto-antibodies (e.g., anti-TSHR-IgG,

anti-IGF-1R-IgG, or both). In some embodiments, a patient in need of treatment for Graves' ophthalmopathy is sero-negative, i.e., does not have detectable auto-antibodies against TSHR, IGF-1R, or both, but may benefit from treatment with an anti-FcRn antibody, antigen-binding fragment, or pharmaceutical composition described herein, as judged by the treating clinician. In some embodiments, a patient in need of treatment for Graves' ophthalmopathy has moderate to severe active disease and has not yet been treated with radiation or surgical therapy. In some embodiments, moderate to severe active disease is defined by clinical parameters, e.g., lid retraction ($\geq$ 2 mm), exophthalmos ($\geq$ 3 mm), diplopia, and/or moderate to severe soft tissue involvement.

One embodiment is a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of an anti-FcRn antibody or an antigen-binding fragment thereof; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of an anti-FcRn antibody or an antigen-binding fragment thereof.

Another embodiment is an anti-FcRn antibody or an antigen-binding fragment thereof for use in a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, the method comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment, or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

Another embodiment is a use of an anti-FcRn antibody or an antigen-binding fragment thereof in a method of treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

Another embodiment is a use of an anti-FcRn antibody or an antigen-binding fragment thereof in the manufacture of a medicament for treating or preventing Graves' ophthalmopathy in a patient in need thereof, comprising administering to the patient (i) a therapeutically effective amount of the antibody or antigen-binding fragment; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein,

an anti-FcRn antibody or antigen-binding fragment acts as a non-competitive inhibitor of IgG in binding to FcRn. In various embodiments, the binding of the antibody or antigen-binding fragment to FcRn inhibits the binding of at least one autoantibody and/or pathogenic antibody to FcRn. In various embodiments, such inhibition promotes clearance (i.e., removal) of the at least one autoantibody and/or pathogenic antibody from the body of the subject. In various embodiments, such inhibition reduces the half-life of the at least one autoantibody and/or pathogenic antibody. In various embodiments, such inhibition reduces the level of the at least one autoantibody and/or pathogenic antibody in the subject and/or in a sample from the subject. In various embodiments, a reduction in the level of the at least one autoantibody and/or pathogenic antibody results in and/or correlates with an improvement in at least one clinical parameter of a disease, disorder, or condition (e.g., Graves' ophthalmopathy).

As used herein, the term "autoantibody" refers to an antibody produced by an organism's immune system that is directed against one or more of the organism's own proteins, tissues, and/or organs. For instance, one or more autoantibodies may be produced by a human patient's immune system when it fails to distinguish between "self" and "non-self." In some embodiments, the autoantibody is a pathogenic antibody (e.g., a pathogenic IgG, e.g., a pathogenic IgG1, IgG2, IgG3, or IgG4). The term "pathogenic antibody," as used herein, refers to an antibody (e.g., an autoantibody) that contributes to the pathogenesis of and/or causes one or more diseases, disorders,

or conditions (e.g., Graves' ophthalmopathy). Examples of such antibodies include, but are not limited to, anti-platelet antibodies, anti-acetylcholine antibodies, anti-nucleic acid antibodies, anti-phospholipid antibodies, anti-collagen antibodies, anti-ganglioside antibodies, and anti-desmoglein antibodies. In various embodiments, the pathogenic antibody is a pathogenic IgG (e.g., a pathogenic IgG1, IgG2, IgG3, or IgG4). In various embodiments, the pathogenic antibody and/or pathogenic IgG is anti-TSHR-IgG. In various embodiments, the pathogenic antibody and/or pathogenic IgG is anti-IGF-1R-IgG. In various embodiments, the pathogenic antibody and/or pathogenic IgG is a combination of anti-TSHR-IgG and anti-IGF-1R-IgG.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein,

an anti-FcRn antibody or antigen-binding fragment can non-competitively inhibit the binding of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) to FcRn at physiological pH (i.e., pH 7.0-7.4). Without wishing to be bound by theory, it is believed that FcRn binds to its ligand (i.e., IgG) and does not substantially show affinity for IgG at physiological pH rather than acidic pH. Thus, in various embodiments, at physiological pH, the anti-FcRn antibody or antigen-binding fragment may act as a non-competitive inhibitor of the binding of IgG to FcRn, and the binding of the anti-FcRn antibody or antigen-binding fragment to FcRn is not influenced by the presence of IgG. Thus, in various embodiments, the anti-FcRn antibody or antigen-binding fragment that binds specifically to FcRn non-competitively with IgG in a pH-independent manner has an advantage over conventional competitive inhibitors (i.e., antibodies that bind to FcRn competitively with IgG) in that it can provide therapeutic or prophylactic effects even at significantly low concentrations by the FcRn-mediated signaling of IgG. In addition, in various embodiments, in the procedure of intracellular migration in a state bound to FcRn, the anti-FcRn antibody or antigen-binding fragment can maintain its binding to FcRn with an affinity higher than IgG in blood. Thus, in various embodiments, the anti-FcRn antibody or antigen-binding fragment can inhibit the binding of IgG to FcRn even in endosomes that are acidic pH

environments in which IgG can bind to FcRn, thereby promoting the clearance of IgG. In various embodiments, the anti-FcRn antibody or antigen-binding fragment is RVT-1401 (also referred to herein as HL161BKN). In some embodiments, the antibody or antigen-binding fragment is RVT-1401, or an antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment comprises three heavy chain CDR amino acid sequences of SEQ ID No: 27 (HCDR1), SEQ ID No: 28 (HCDR2), SEQ ID No: 29 (HCDR3); and three light chain CDR amino acid sequences of SEQ ID No: 30 (LCDR1), SEQ ID No: 31 (LCDR2), SEQ ID No: 32 (LCDR3). In some embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region amino acid sequence of SEQ ID No: 6; and a light chain variable region amino acid sequence of SEQ ID No: 16. In some embodiments, the antibody or antigen-binding fragment comprises a heavy chain amino acid sequence of SEQ ID No: 46; and a light chain amino acid sequence of SEQ ID No: 48.

Binding “affinity” refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites. In general, the more interactions, the stronger the affinity.

As used herein, the term "specific," "specifically binds," and "binds specifically" refers to a binding reaction between an antibody or an antigen-binding fragment thereof (e.g., an anti-FcRn antibody or an antigen-binding fragment thereof) and a target antigen (e.g., FcRn) in a heterogeneous population of proteins and other biologics. Antibodies can be tested for specificity of binding by comparing binding to an appropriate antigen with binding to an alternate antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen with at least 2 times, at least 5 times, or at least 10 times (or more) more affinity than to the alternate antigen or antigen mixture, then it is considered to be specific.

A “specific antibody” or a “target-specific antibody” is one that only binds the target antigen (e.g., FcRn), but does not bind (or exhibits minimal binding) to other antigens. In some

embodiments, an antibody or an antigen-binding fragment thereof that specifically binds the target antigen (e.g., FcRn) has a K_D of less than $1x10^{-6}$ M, less than $1x10^{-7}$ M, less than $1x10^{-8}$ M, less than $1x10^{-9}$ M, less than $1x10^{-10}$ M, less than $1x10^{-11}$ M, less than $1x10^{-12}$ M, or less than $1x10^{-13}$ M at pH 6.0 or pH 7.4. In some embodiments, the K_D is about 0.01 nM to about 2 nM at pH 6.0 or pH 7.4. In some embodiments, the K_D is about 300 pM or less to about 2 nM or less at pH 7.4. In some embodiments, the K_D is about 2 nM or less to 900 pM or less at pH 6.0.

As used herein, the term "K_D" refers to the equilibrium dissociation constant for antibody-antigen binding, which is obtained from the ratio of k_d to k_a (i.e., k_d/k_a) and is generally expressed as a molar concentration (M). The term "k_{assoc}" or "k_a" refers to the association rate of a particular antibody-antigen interaction, whereas the term "k_{dis}" or "k_d" refers to the dissociation rate of a particular antibody-antigen interaction. The measurement of k_d and/or k_a can be performed at 25°C or 37°C. K_D values for antibodies and antigen-binding fragments can be determined using methods well established in the art (see, e.g., Pollard, Mol. Biol. Cell 21(23):4061-7, 2010). In some embodiments, the K_D is measured by direct binding and/or competition binding assays (e.g., surface plasmon resonance and/or competition ELISA). In some embodiments, the K_D is measured by surface plasmon resonance (e.g., human FcRn-immobilized surface plasmon resonance). In some embodiments, the K_D of an anti-FcRn antibody or antigen-binding fragment disclosed herein is measured by human FcRn-immobilized surface plasmon resonance.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody or antigen-binding fragment has a K_D (dissociation constant) of about 0.01 to 2 nM at pH 6.0 and pH 7.4, as determined by, e.g., surface plasmon resonance. In some embodiments, the anti-FcRn antibody or antigen-binding fragment has a K_D from about 300 pM or less to about 2 nM or less at pH 7.4 and/or has a K_D from about 2 nM or less to about 900 pM or less at pH 6.0, as determined by, e.g., surface plasmon resonance. In some embodiments, the anti-FcRn antibody or antigen-binding fragment binds to the outside of cells and when bound maintains its binding to endosomes. In some embodiments, the anti-FcRn antibody or antigen-

binding fragment effectively blocks the binding of one or more autoantibodies to FcRn (e.g., human FcRn), as determined by, e.g., a blocking assay performed using human FcRn-expressing cells and FACS.

As used herein, the term "anti-FcRn antibody" or "antibody that binds specifically to FcRn" refers to any form of an antibody or an antigen-binding fragment thereof that binds specifically to FcRn, e.g., those binding with a K_D of less than 2 nM at pH 6.0 or pH 7.4, as determined by, e.g., surface plasmon resonance, e.g., human FcRn-immobilized surface plasmon resonance. The term encompasses monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, and biologically functional fragments so long as they bind specifically to FcRn.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody or antigen-binding fragment comprises:

CDR1 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 21, 24, 27, 30, 33, 36, 39, and 42;

CDR2 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 22, 25, 28, 31, 34, 37, 40, and 43; and

CDR3 comprising an amino acid sequence that is at least 90% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 23, 26, 29, 32, 35, 38, 41, and 44.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody or antigen-binding fragment comprises:

CDR1 comprising an amino acid sequence that is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 21, 24, 27, 30,

33, 36, 39, and 42;

CDR2 comprising an amino acid sequence that is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 22, 25, 28, 31, 34, 37, 40, and 43; and

CDR3 comprising an amino acid sequence that is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to one or more amino acid sequences selected from the group consisting of SEQ ID Nos: 23, 26, 29, 32, 35, 38, 41, and 44.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody or antigen-binding fragment may comprise one or more amino acid deletions, additions, or substitutions in the amino acid sequences described herein.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody or antigen-binding fragment may comprise amino acid sequences identical to or having homology with the amino acid sequences described herein. The term “identity” or “homology” refers to a relationship between the sequences of two or more polypeptides, as determined by comparing the sequences. The term "identity" also means the degree of sequence relatedness between the polypeptides, as determined by the number of matches between strings of two or more amino acid residues. The percent “identity” between the two sequences is a function of the number of identical positions shared by the sequences (i.e., percent identity equals number of identical positions/total number of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are

entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters. Additionally, or alternatively, the amino acid sequences disclosed herein can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. For example, such searches can be performed using the BLAST program of Altschul et al. (J. Mol. Biol. 215:403-10, 1990).

Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues that are the same (i.e., 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 10 amino acids in length, or more preferably over a region that is about 20, 50, 200 or more amino acids in length. In some embodiments, the anti-FcRn antibodies and antigen-binding fragments described herein comprise at least one amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20-48. In some embodiments, the anti-FcRn antibodies and antigen-binding fragments described herein comprise at least one amino acid sequence that is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to a sequence selected from the group consisting of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20-48.

In some embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising:

CDR1 comprising an amino acid sequence of SEQ ID No: 21, CDR2 comprising an amino

acid sequence of SEQ ID No: 22, and CDR3 comprising an amino acid sequence of SEQ ID No: 23;

CDR1 comprising an amino acid sequence of SEQ ID No: 27, CDR2 comprising an amino acid sequence of SEQ ID No: 28, and CDR3 comprising an amino acid sequence of SEQ ID No: 29;

CDR1 comprising an amino acid sequence of SEQ ID No: 33, CDR2 comprising an amino acid sequence of SEQ ID No: 34, and CDR3 comprising an amino acid sequence of SEQ ID No: 35; or

CDR1 comprising an amino acid sequence of SEQ ID No: 39, CDR2 comprising an amino acid sequence of SEQ ID No: 40, and CDR3 comprising an amino acid sequence of SEQ ID No: 41.

In some embodiments, the antibody or antigen-binding fragment comprises a light chain variable region comprising:

CDR1 comprising an amino acid sequence of SEQ ID No: 24, CDR2 comprising an amino acid sequence of SEQ ID No: 25, and CDR3 comprising an amino acid sequence of SEQ ID No: 26;

CDR1 comprising an amino acid sequence of SEQ ID No: 30, CDR2 comprising an amino acid sequence of SEQ ID No: 31, and CDR3 comprising an amino acid sequence of SEQ ID No: 32;

CDR1 comprising an amino acid sequence of SEQ ID No: 36, CDR2 comprising an amino acid sequence of SEQ ID No: 37, and CDR3 comprising an amino acid sequence of SEQ ID No: 38; or

CDR1 comprising an amino acid sequence of SEQ ID No: 42, CDR2 comprising an amino acid sequence of SEQ ID No: 43, and CDR3 comprising an amino acid sequence of SEQ ID No: 44.

In some embodiments, the antibody or antigen-binding fragment comprises one or more

heavy chain variable regions and one or more light chain variable regions selected from the group consisting of:

heavy chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 21 (HCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 22 (HCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 23 (HCDR3); and light chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 24 (LCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 25 (LCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 26 (LCDR3);

heavy chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 27 (HCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 28 (HCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 29 (HCDR3); and light chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 30 (LCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 31 (LCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 32 (LCDR3);

heavy chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 33 (HCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 34 (HCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 35 (HCDR3); and light chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 36 (LCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 37 (LCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 38 (LCDR3); and

heavy chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 39 (HCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 40 (HCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 41 (HCDR3); and light chain variable region comprising CDR1 comprising an amino acid sequence of SEQ ID No: 42 (LCDR1), CDR2 comprising an amino acid sequence of SEQ ID No: 43 (LCDR2), and CDR3 comprising an amino acid sequence of SEQ ID No: 44 (LCDR3).

In some embodiments, the antibody or antigen-binding fragment comprises one or more heavy chain variable regions and/or one or more light chain variable regions comprising one or more amino acid sequences selected from the group consisting of amino acid sequences of SEQ ID Nos: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20.

In some embodiments, the antibody or antigen-binding fragment comprises heavy chain variable region comprising an amino acid sequence of SEQ ID Nos: 2, 4, 6, 8, or 10, and/or light chain variable region comprising an amino acid sequence of SEQ ID Nos: 12, 14, 16, 18, or 20.

In some embodiments, the antibody or antigen-binding fragment comprises one or more heavy chain variable regions and one or more light chain variable regions selected from the group consisting of:

heavy chain variable region comprising an amino acid sequence of SEQ ID No: 2 and light chain variable region comprising an amino acid sequence of SEQ ID No: 12;

heavy chain variable region comprising an amino acid sequence of SEQ ID No: 4 and light chain variable region comprising an amino acid sequence of SEQ ID No: 14;

heavy chain variable region comprising an amino acid sequence of SEQ ID No: 6 and light chain variable region comprising an amino acid sequence of SEQ ID No: 16;

heavy chain variable region comprising an amino acid sequence of SEQ ID No: 8 and light chain variable region comprising an amino acid sequence of SEQ ID No: 18; and

heavy chain variable region comprising an amino acid sequence of SEQ ID No: 10 and light chain variable region comprising an amino acid sequence of SEQ ID No: 20.

The terms “fragment,” “antibody fragment,” and “antigen-binding fragment,” as used herein in reference to an antibody, all refer to one or more fragments of a full-length antibody that retain the ability to specifically bind to the target antigen (e.g., FcRn) and/or provide a function of the full-length antibody (e.g., non-competitive interference with the binding of IgG to FcRn). Antigen-binding fragments can also be present in larger macromolecules, e.g., bispecific, trispecific, and multispecific antibodies.

Examples of antigen-binding fragments include, but are not limited to, single-chain antibodies, bispecific, trispecific, and multispecific antibodies such as diabodies, triabodies and tetrabodies, Fab fragments, $F(ab')_2$ fragments, Fd, scFv, domain antibodies, dual-specific antibodies, minibodies, scap (sterol regulatory binding protein cleavage activating protein), chelating recombinant antibodies, tribodies or bibodies, intrabodies, nanobodies, small modular immunopharmaceuticals (SMIP), binding-domain immunoglobulin fusion proteins, camelized antibodies, VHH containing antibodies, IgD antibodies, IgE antibodies, IgM antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies, derivatives in antibody constant regions, and synthetic antibodies based on protein scaffolds that have the ability to bind to FcRn. In some embodiments, an antigen-binding fragment shows the same or similar properties as those of the full-length antibody. Without limitation, an antigen-binding fragment can be produced by any suitable method known in the art. For instance, the various antigen-binding fragments described herein can be produced by enzymatic or chemical modification of full-length antibodies, synthesized de novo using recombinant DNA methodologies (e.g., scFv), or identified using phage display libraries (see, e.g., Pini and Bracci, Curr. Protein Pept. Sci. 1(2):155-69, 2000). Antigen-binding fragments can be screened for utility (e.g., specificity, binding affinity, activity) in the same manner as are full-length antibodies.

In addition, antibodies or antigen-binding fragments having a mutation in the variable and/or constant region may be used in the therapeutic methods, uses, and compositions described herein. Examples of such antibodies or antigen-binding fragments include antibodies having a conservative substitution of an amino acid residue in the variable region and/or constant region. As used herein, the term "conservative substitution" refers to a substitution with another amino acid residue having properties similar to those of the original amino acid residue. For example, lysine, arginine and histidine have similar properties in that they have a basic side-chain, and aspartic acid and glutamic acid have similar properties in that they have an acidic side chain. In addition, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine and tryptophan have

similar properties in that they have an uncharged polar side-chain, and alanine, valine, leucine, threonine, isoleucine, proline, phenylalanine and methionine have similar properties in that they have a non-polar side-chain. Also, tyrosine, phenylalanine, tryptophan and histidine have similar properties in that they have an aromatic side-chain. Thus, it will be obvious to those skilled in the art that, even when substitution of amino acid residues in groups showing similar properties as described above occurs, it will likely show no significant change in the properties of the antibody or antigen-binding fragment.

In addition, in some embodiments, the antibody or antigen-binding fragment may be conjugated to another substance (e.g., a therapeutic agent or a detectable label). Substances that may be conjugated to the antibody or antigen-binding fragment include but are not limited to therapeutic agents that are generally used for the treatment of Graves' ophthalmopathy (e.g., a standard of care agent, a beta-blocker, an antithyroid drug (e.g., methimazole)), substances capable of inhibiting the activity of FcRn, and a moiety that is physically associated with the antibody or antigen-binding fragment to improve its stabilization and/or retention in circulation, for example, in blood, serum, lymph, or other tissues. For example, the antibody or antigen-binding fragment can be associated with a polymer, e.g., a non-antigenic polymer such as polyalkylene oxide or polyethylene oxide. Suitable polymers will vary substantially by weight. Polymers having molecular number average weights ranging from about 200 to about 35,000 (or about 1,000 to about 15,000, and 2,000 to about 12,500) can be used. For example, the antibody or antigen-binding fragment can be conjugated to water soluble polymers, e.g., hydrophilic polyvinyl polymers, e.g., polyvinylalcohol and polyvinylpyrrolidone. Non-limiting examples of such polymers include, but are not limited to, polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the antibody or antigen-binding fragment comprises a heavy chain variable region

comprising an amino acid sequence of SEQ ID No: 27 (HCDR1), an amino acid sequence of SEQ ID No: 28 (HCDR2), and an amino acid sequence of SEQ ID No: 29 (HCDR3); and a light chain variable region comprising an amino acid sequence of SEQ ID No: 30 (LCDR1), an amino acid sequence of SEQ ID No: 31 (LCDR2), and an amino acid sequence of SEQ ID No: 32 (LCDR3).

In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence of SEQ ID No: 16. In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 16. In various embodiments, the antibody or antigen-binding fragment binds to FcRn with a K_D (dissociation constant) of 0.01 to 2 nM at pH 6.0 or pH 7.4, as measured by, e.g., surface plasmon resonance.

In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain amino acid sequence of SEQ ID No: 46, or a sequence that is at least 90% identical to SEQ ID No: 46. In various embodiments, the antibody or antigen-binding fragment comprises a light chain amino acid sequence of SEQ ID No: 48, or a sequence that is at least 90% identical to SEQ ID No: 48. In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain amino acid sequence of SEQ ID No: 46, and a light chain amino acid sequence of SEQ ID No: 48. In various embodiments, the antibody or antigen-binding fragment comprises a heavy chain amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID No: 46, and a light chain amino acid sequence that is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% identical to SEQ ID No: 48.

RVT-1401 (also referred to herein as HL161BKN) is an example of an anti-FcRn antibody. In some embodiments, the antibody or antigen-binding fragment is RVT-1401, or an antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment

comprises the three heavy chain CDR amino acid sequences of RVT-1401 (HCDR1 (SEQ ID No: 27), HCDR2 (SEQ ID No: 28), HCDR3 (SEQ ID No: 29)); and the three light chain CDR amino acid sequences of RVT-1401 (LCDR1 (SEQ ID No: 30), LCDR2 (SEQ ID No: 31), LCDR3 (SEQ ID No: 32)). In some embodiments, the antibody or antigen-binding fragment comprises the heavy chain variable region amino acid sequence of RVT-1401 (SEQ ID No: 6); and the light chain variable region amino acid sequence of RVT-1401 (SEQ ID No: 16). In some embodiments, the antibody or antigen-binding fragment comprises the heavy chain amino acid sequence of RVT-1401 (SEQ ID No: 46); and the light chain amino acid sequence of RVT-1401 (SEQ ID No: 48).

In various embodiments of the therapeutic methods and uses disclosed herein, the antibody or antigen-binding fragment is administered alone. In various embodiments, the antibody or antigen-binding fragment is administered in combination with at least one additional therapeutic agent (e.g., a beta-blocker, an antithyroid drug (e.g., methimazole)). In various embodiments, the at least one additional therapeutic agent may comprise or consist of a standard-of-care agent for the particular condition being treated (e.g., Graves' ophthalmopathy).

Administered "in combination" or "co-administration," as used herein, means that two or more different treatments are delivered to a subject during the subject's affliction with a medical condition (e.g., Graves' ophthalmopathy). For example, in some embodiments, the two or more treatments are delivered after the subject has been diagnosed with a disease or disorder, and before the disease or disorder has been cured or eliminated, or when a subject is identified as being at risk but before the subject has developed symptoms of the disease. In some embodiments, the delivery of one treatment is still occurring when the delivery of the second treatment begins, so that there is overlap. In some embodiments, the first and second treatment are initiated at the same time. These types of delivery are sometimes referred to herein as "simultaneous," "concurrent," or "concomitant" delivery. In other embodiments, the delivery of one treatment ends before delivery of the second treatment begins. This type of delivery is sometimes referred

to herein as "successive" or "sequential" delivery. In some embodiments, the antibody or antigen-binding fragment and the at least at one additional therapeutic agent are administered simultaneously. In some embodiments, the antibody or antigen-binding fragment and the at least at one additional therapeutic agent are administered sequentially.

In some embodiments, the two treatments (e.g., an anti-FcRn antibody or antigen-binding fragment and a second therapeutic agent) are comprised in the same composition. Such compositions may be administered in any appropriate form and by any suitable route. In other embodiments, the two treatments (e.g., an anti-FcRn antibody or antigen-binding fragment and a second therapeutic agent) are administered in separate compositions, in any appropriate form and by any suitable route. For example, a composition comprising an anti-FcRn antibody or a antigen-binding fragment and a composition comprising a second therapeutic agent may be administered concurrently or sequentially, in any order at different points in time; in either case, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect.

The term "agent," as used herein, refers to a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials. The term "therapeutic agent" or "drug" refers to an agent that is capable of modulating a biological process and/or has biological activity. The anti-FcRn antibodies and antigen-binding fragments described herein are examples of therapeutic agents.

As used herein, the term "standard-of-care agent" refers to any therapeutic agent or other form of therapy that is accepted as a proper treatment for a certain type of disease (e.g., Graves' ophthalmopathy). The term "standard dosage" or "standard dosing regimen," as used herein, refers to any usual or routine dosing regimen for a therapeutic agent, e.g., a regimen proposed by the manufacturer, approved by regulatory authorities, or otherwise tested in human subjects to meet the average patient's needs.

Also provided herein are pharmaceutical compositions comprising the anti-FcRn antibody or an antigen-binding fragment thereof formulated together with at least one pharmaceutically acceptable carrier. The compositions may also contain one or more additional therapeutic agents that are suitable for treating or preventing, for example, Graves' ophthalmopathy. Methods of formulating pharmaceutical compositions and suitable formulations are known in the art (see, e.g., "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA). Appropriate formulation may depend on the route of administration.

As used herein, a "pharmaceutical composition" refers to a preparation of an anti-FcRn antibody or an antigen-binding fragment thereof in addition to other components suitable for administration to a patient, such as a pharmaceutically acceptable carrier and/or excipient. The pharmaceutical compositions provided herein may be suitable for administration *in vitro* and/or *in vivo*. In some embodiments, the pharmaceutical composition may comprise a pharmaceutically acceptable carrier, excipient, and the like, which are well known in the art. In some embodiments, the pharmaceutical compositions provided herein are in such form as to permit administration and subsequently provide the intended biological activity of the active ingredient(s) and/or to achieve a therapeutic effect. The pharmaceutical compositions provided herein preferably contain no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

As used herein, the terms "pharmaceutically acceptable carrier" and "physiologically acceptable carrier," which may be used interchangeably, refer to a carrier, diluent, or excipient that does not cause significant irritation to a subject and does not abrogate the biological activity and properties of the administered antibody or antigen-binding fragment. Thus, pharmaceutically acceptable carriers should be compatible with the active ingredient such as the antibody or an antigen-binding fragment thereof and may include physiological saline, sterile water, Ringer's solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, ethanol, or a mixture of two or more thereof. Pharmaceutically acceptable carriers may also enhance or stabilize the

composition, or can be used to facilitate preparation of the composition. Pharmaceutically acceptable carriers can include other conventional additives, such as antioxidants, buffers, solvents, bacteriostatic agents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The carrier may be selected to minimize adverse side effects in the subject, and/or to minimize degradation of the active ingredient(s).

As used herein, the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Formulations for parenteral administration can, for example, contain excipients such as sterile water or saline, polyalkylene glycols such as polyethylene glycol, vegetable oils, or hydrogenated napthalenes. Other excipients include, but are not limited to, calcium bicarbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, ethylene-vinyl acetate co-polymer particles, and surfactants, including, for example, polysorbate 20.

In various embodiments of the therapeutic methods, uses, and compositions disclosed herein, the anti-FcRn antibody, antigen-binding fragment, or pharmaceutical composition can be administered by a variety of methods known in the art. The route and/or mode of administration may vary depending upon the desired results. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered by oral, intravenous, intramuscular, intra-arterial, intramedullary, intradural, intracardial, transdermal, subcutaneous, intraperitoneal, gastrointestinal, sublingual, or local routes. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered orally or parenterally. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered parenterally, e.g., intravenously or subcutaneously (e.g., by injection or infusion). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered subcutaneously (e.g., by injection). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as one or more subcutaneous

injections. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as one subcutaneous injection. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered as two consecutive subcutaneous injections. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is delivered via a syringe, a catheter, a pump delivery system, or a stent. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is delivered via a syringe (e.g., a pre-filled syringe). Depending on the route of administration, the active compound(s), i.e., the anti-FcRn antibody or antigen-binding fragment, may be coated in a material to protect the compound(s) from the action of acids and other natural conditions that may inactivate the compound(s).

An antibody, antigen-binding fragment, or pharmaceutical composition may be formulated as various forms such as a powder, tablet, capsule, liquid, injection, ointment, or syrup, and/or comprised in a single-dosage or multi-dosage container such as a sealed ampoule, vial, or syringe. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated as an injectable form. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated as an aqueous solution, suspension, or emulsion, with one or more excipients, diluents, dispersants, surfactants, binders, and/or lubricants. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is comprised in a syringe (e.g., a pre-filled syringe). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is contained in a syringe prior to administration.

Dosage regimens for the anti-FcRn antibody or antigen-binding fragment, either alone or in combination with one or more additional therapeutic agents, may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus of the anti-FcRn antibody or antigen-binding fragment may be administered at one time, several divided doses may be administered over a predetermined period of time, or the dose of the anti-FcRn antibody

or antigen-binding fragment may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. For any particular subject, specific dosage regimens may be adjusted over time according to the individual's need, and the professional judgment of the treating clinician. For instance, in some embodiments, the dose of the anti-FcRn antibody or antigen-binding fragment can be suitably determined by taking into consideration the patient's severity, condition, age, case history, and the like.

The anti-FcRn antibody or antigen-binding fragment may be formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Parenteral compositions, for example, may be formulated in dosage unit form for ease of administration and uniformity of dosage. As used herein, "dosage unit form" refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated in dosage unit form. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated in dosage unit form for subcutaneous administration. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated in dosage unit form for administration as one or more subcutaneous injections (e.g., one subcutaneous injection or two consecutive subcutaneous injections). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is formulated in dosage unit form (e.g., as one or more subcutaneous injections) for self-administration by the patient and/or for administration by a treating clinician.

Dosage values for the anti-FcRn antibody or antigen-binding fragment, compositions comprising the anti-FcRn antibody or antigen-binding fragment, and/or any additional therapeutic agent(s), may be selected based on the unique characteristics of the active compound(s) and the particular therapeutic effect to be achieved. A physician or veterinarian can start doses of the

antibodies or antigen-binding fragments at levels lower than those required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. A physician or veterinarian can also start doses of the antibodies or antigen-binding fragments at levels higher than those required to achieve the desired therapeutic effect and gradually decrease the dosage until the desired effect is achieved. In general, effective doses of the antibodies or antigen-binding fragments for the treatment of Graves' ophthalmopathy may vary depending upon many different factors, including whether the treatment is prophylactic or therapeutic. The selected dosage level may also depend upon a variety of pharmacokinetic factors including the activity of the particular compositions employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors. Treatment dosages may be titrated to optimize safety and efficacy. In some embodiments, the treatment may be administered once or several times. Intermittent and/or chronic (continuous) dosing strategies may be applied in view of the condition of the particular patient.

In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is employed in the methods, uses, and pharmaceutical compositions of the present disclosure.

As used herein, the terms "therapeutically effective amount" and "therapeutically effective dose" are used interchangeably herein to refer to an amount sufficient to decrease at least one symptom or measurable parameter associated with a medical condition or infirmity, to normalize body functions in a disease or disorder that results in the impairment of specific bodily functions; and/or to provide improvement in, or slow the progression of, one or more clinically measured parameters of a disease. A therapeutically effective amount may, for example, be sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence

of one or more symptoms of Grave's ophthalmopathy. A therapeutically effective amount, as well as a therapeutically effective frequency of administration, can be determined by methods known in the art and discussed herein. In some embodiments of the methods, uses, and compositions described herein, the anti-FcRn antibody or antigen-binding fragment is in and/or is administered in an amount that is therapeutically effective when administered as a single agent. In some embodiments, the anti-FcRn antibody or antigen-binding fragment and at least one additional therapeutic agent are each administered in an amount that is therapeutically effective when the agents are used in combination.

In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in a patient and/or in a sample from a patient (e.g., a Graves' ophthalmopathy patient). In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the level of at least one IgG in a patient and/or in a sample from a patient (e.g., a Graves' ophthalmopathy patient). In some embodiments, the at least one IgG comprises anti-TSHR IgG and/or anti-IGF-1R IgG. In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the level of anti-TSHR IgG in the patient and/or in a sample from the patient by at least about 30%, about 40%, about 50%, about 60%, about 70%, or about 80% (i.e., relative to the level of anti-TSHR IgG prior to treatment with the anti-FcRn antibody or antigen-binding fragment). In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the level of anti-IGF-1R IgG in the patient and/or in a sample from the patient by at least about 30%, about 40%, about 50%, about 60%, about 70%, or about 80% (i.e., relative to the level of anti-IGF-1R IgG prior to treatment with the anti-FcRn antibody or antigen-binding fragment).

In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the level of total serum IgG in a patient and/or in a sample from a patient (e.g., a Graves' ophthalmopathy patient) by at least about 40%, about 50%, about 60%, about 70%, or about 80% (i.e., relative to the level of total serum IgG prior to treatment with the anti-FcRn antibody or antigen-binding fragment). In some embodiments, a therapeutically effective amount of the anti-FcRn antibody or antigen-binding fragment is the amount required to reduce the serum endogenous IgG concentration in a patient and/or in a sample from a patient (e.g., a Graves' ophthalmopathy patient) to less than about 75% of pretreatment values.

The phrase "total IgG level" or "level of total serum IgG," as used herein, refers to the serum endogenous IgG concentration, e.g., in a patient or in a biological sample (e.g., a blood sample) from a patient.

The phrase "level of at least one autoantibody," as used herein, refers to the serum endogenous concentration of the at least one autoantibody, e.g., in a patient or in a biological sample from a patient.

The phrase "level of at least one IgG," as used herein, refers to the serum endogenous concentration of the at least one IgG, e.g., in a patient or in a biological sample from a patient. In some embodiments, the at least one IgG comprises a pathogenic IgG. In some embodiments, the at least one IgG comprises serum IgG1. In some embodiments, the at least one IgG comprises serum IgG2. In some embodiments, the at least one IgG comprises serum IgG3. In some embodiments, the at least one IgG comprises serum IgG4. In some embodiments, the at least one IgG comprises anti-TSHR IgG, anti-IGF-1R IgG, or both.

The phrase "sero-negative," as used herein, may be used to describe a patient who does not have detectable auto-antibodies against TSHR, IGF-1R, or both, but may benefit from treatment with an anti-FcRn antibody, antigen-binding fragment, or pharmaceutical composition described herein, as judged by the treating clinician. In some embodiments, a patient suitable for

treatment with an anti-FcRn antibody, antigen-binding fragment, or pharmaceutical composition described herein is sero-negative. In some embodiments, a patient in need of treatment with an anti-FcRn antibody, antigen-binding fragment, or pharmaceutical composition described herein is sero-negative. In some embodiments, a sero-negative patient does not have a detectable level of anti-TSHR IgG. In some embodiments, a sero-negative patient does not have a detectable level of anti-IGF-1R IgG. In some embodiments, a sero-negative patient does not have a detectable level of anti-TSHR IgG or anti-IGF-1R IgG. In some embodiments, a sero-negative patient does not have a detectable level of anti-TSHR IgG and anti-IGF-1R IgG.

The term "about" or "approximately," as used herein in the context of numerical values and ranges, refers to values or ranges that approximate or are close to the recited values or ranges such that the embodiment may perform as intended, as is apparent to the skilled person from the teachings contained herein. These terms encompass values beyond those resulting from systematic error. In some embodiments, "about" or "approximately" means plus or minus 10% of a numerical amount.

In various embodiments of the therapeutic methods and uses disclosed herein, the antibody or antigen-binding fragment is administered to a patient as a fixed dose. In various embodiments of the therapeutic methods and uses disclosed herein, the antibody or antigen-binding fragment is administered to a patient as a weight-based dose, i.e., a dose dependent on the patient's bodyweight. In various embodiments of the therapeutic methods and uses disclosed herein, the antibody or antigen-binding fragment is administered to a patient as a body surface area-based dose, i.e., a dose dependent on the patient's body surface area (BSA). In various embodiments, the dose administered to the patient comprises a therapeutically effective amount of the antibody or antigen-binding fragment.

In some embodiments, the antibody or antigen-binding fragment is administered to patient at dose of about 100 mg to about 1000 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 100 mg, about 150 mg, about

200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg. In some embodiments, the antibody or antigen-binding fragment is administered to patient at dose of about 100 mg to about 1000 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 to about 450 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, or about 450 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 to about 450 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 to about 300 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, or about 300 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, or about 280 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 255 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 200 to about 300 mg (e.g., about 255 mg) once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 300 to about 400 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, or about 400 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 320 mg, about 330 mg, about 340 mg, about 350 mg, or about 360 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 340 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 300 to about 400 mg (e.g., about 340 mg) once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 400 to about 500 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 400 to about 500 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 500 to about 600 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 500 to about 600 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 600 to about 800 mg. In some embodiments, the antibody or antigen-

binding fragment is administered to the patient at a dose of about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, or about 800 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 600 to about 800 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 550 to about 650 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, or about 650 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 550 to about 650 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 650 to about 750 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, or about 750 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 660 mg, about 670 mg, about 680 mg, about 690 mg, or about 700 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 680 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 650 to about 750 mg (e.g., about 680 mg) once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 750 to about 850 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 750 mg, about 760 mg, about

770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, or about 850 mg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 750 to about 850 mg once weekly or once every 2 weeks.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at one or more doses (e.g., two or more different doses). For example, in some embodiments, the antibody or antigen-binding fragment is administered to the patient at two different doses, e.g., at least one higher dose, followed by at least one lower dose. A higher dose (e.g., a higher dose of two different doses) may be referred to herein as an "induction" dose, i.e., a dose capable of reducing the level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in a patient and/or a sample from a patient. A lower dose (e.g., a lower dose of two different doses) may be referred to herein as a "maintenance" dose, i.e., a dose capable of maintaining the reduced level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in the patient and/or a sample from the patient following at least one induction dose of an antibody or antigen-binding fragment (e.g., about 20-80% of pretreatment (pre-induction dose) values). In some embodiments, a maintenance dose maintains the level of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in the patient and/or a sample from the patient at about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% of pretreatment (pre-induction dose) values.

In some embodiments, at least one higher dose and/or induction dose is about 680 mg per dose or more (e.g., about 700 mg per dose, about 720 mg per dose, about 750 mg per dose, or more). In some embodiments, the at least one higher dose and/or induction dose is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses at about 680 mg per dose or more (e.g., about 700 mg per dose, about 720 mg per dose, about 750 mg per dose, or more). In some embodiments, the at least one higher dose and/or induction dose is about 3 doses at about

680 mg per dose or more (e.g., about 700 mg per dose, about 720 mg per dose, about 750 mg per dose, or more). In some embodiments, the at least one higher dose and/or induction dose is administered to the patient once, once weekly, once every 2 weeks, or once monthly. In some embodiments, the at least one higher dose and/or induction dose is administered to the patient intravenously. In some embodiments, the at least one higher dose and/or induction dose is administered to the patient subcutaneously. In some embodiments, each higher dose is administered to the patient as one or more subcutaneous injections. In some embodiments, each higher dose is administered to the patient as two consecutive subcutaneous injections.

In some embodiments, at least one lower dose and/or maintenance dose is about 340 mg per dose. In some embodiments, the at least one lower dose and/or maintenance dose is about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses at about 340 mg per dose. In some embodiments, the at least one lower dose and/or maintenance dose is about 3 doses at about 340 mg per dose. In some embodiments, the at least one lower dose and/or maintenance dose is administered to the patient once, once weekly, once every 2 weeks, or once monthly. In some embodiments, the at least one lower dose and/or maintenance dose is administered to the patient subcutaneously. In some embodiments, each lower dose is administered to the patient as one or more subcutaneous injections. In some embodiments, each lower dose is administered to the patient as one subcutaneous injection.

In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 1 mg/kg to about 2000 mg/kg bodyweight. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 1 mg/kg to about 200 mg/kg, about 200 mg/kg to about 400 mg/kg, about 400 mg/kg to about 600 mg/kg, about 600 mg/kg to about 800 mg/kg, about 800 mg/kg to about 1000 mg/kg, about 1000 mg/kg to about 1200 mg/kg, about 1200 mg/kg to about 1400 mg/kg, about 1400 mg/kg to about 1600 mg/kg, about 1600 mg/kg to about 1800 mg/kg, or about 1800 mg/kg to about 2000 mg/kg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a

dose of about 1 mg/kg to about 200 mg/kg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 1 mg/kg, about 10 mg/kg, about 20 mg/kg, about 30 mg/kg, about 40 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 110 mg/kg, about 120 mg/kg, about 130 mg/kg, about 140 mg/kg, about 150 mg/kg, about 160 mg/kg, about 170 mg/kg, about 180 mg/kg, about 190 mg/kg, or about 200 mg/kg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 1 mg/kg to about 40 mg/kg. In some embodiments, the antibody or antigen-binding fragment is administered to the patient at a dose of about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, or about 40 mg/kg.

The frequency with which the antibody or antigen-binding fragment is administered to the patient, as a single agent or in combination with one or more additional therapeutic agents, may be once or more than once. In some embodiments, the antibody or antigen-binding fragment is administered on a single occasion. In some embodiments, the antibody or antigen-binding fragment is administered on multiple occasions. Intervals between dosages can be, e.g., daily, weekly, bi-weekly, monthly, or yearly. Intervals can also be irregular, e.g., based on measuring blood levels of the antibody or antigen-binding fragment in the patient in order to maintain a relatively consistent plasma concentration of the antibody or antigen-binding fragment, or based on measuring levels of at least one autoantibody and/or pathogenic antibody (e.g., at least one IgG) in order to maintain a reduced level of the at least one autoantibody and/or pathogenic antibody (e.g., the at least one IgG) so as to provide the desired therapeutic or prophylactic effect. Alternatively, in some embodiments, the antibody or antigen-binding fragment can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency may vary depending on the half-life of the antibody or antigen-binding fragment in the patient. The dosage and frequency of administration may also vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications,

a relatively low dosage may be administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively higher dosage at relatively shorter intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of one or more symptoms of disease. Thereafter, the patient may be administered a lower, e.g., prophylactic regime.

In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once or more than once over a period of about 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 18 months, 24 months, 30 months, 36 months, or longer.

In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 20 weeks, at least 24 weeks, at least 30 weeks, at least 40 weeks, at least 50 weeks, at least 60 weeks, at least 70 weeks, at least 76 weeks, at least 80 weeks, or longer. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for 6 to 76 weeks, or any time period in between. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 6 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 12 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 24 weeks. In some embodiments, the

antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 26 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 52 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly for at least 76 weeks or more. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for the entire active/inflammatory phase of Graves' ophthalmopathy, or a portion thereof. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for about 2 years, about 3 years, or any period in between. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for about 2 to about 3 years (e.g., about 2 years, about 2.5 years, about 3 years). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for less than about 2 years (e.g., about 1.5 years or less, about 1 year or less, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for more than about 3 years (e.g., about 3.5 years or more, about 4 years or more, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once weekly for only a portion of the active/inflammatory phase of Graves' ophthalmopathy (e.g., half or a majority of the active/inflammatory phase). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly until sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence of one or more symptoms of Grave's ophthalmopathy.

In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once weekly as one subcutaneous injection. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is

administered to the patient once weekly as two or more consecutive subcutaneous injections (e.g., two consecutive subcutaneous injections). The term "consecutive," as used herein in the context of subcutaneous injections (or other routes of administration), refers to two or more subcutaneous injections administered one after another, but sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. In some embodiments, consecutive subcutaneous injections are administered within about 30 seconds, within about 1 minute, within about 2 minutes, within about 5 minutes, within about 10 minutes, within about 30 minutes, within about 1 hour, within about 2 hours, or within about 5 hours of one another.

In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks (bi-weekly). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 20 weeks, at least 24 weeks, at least 30 weeks, at least 40 weeks, at least 50 weeks, at least 60 weeks, at least 70 weeks, at least 76 weeks, at least 80 weeks, or longer. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for 6 to 76 weeks, or any time period in between. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 6 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 12 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 24 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 26 weeks. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks for at least 52 weeks. In some embodiments, the antibody, antigen-binding fragment, or

pharmaceutical composition is administered to the patient once every 2 weeks for at least 76 weeks or more. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for the entire active/inflammatory phase of Graves' ophthalmopathy, or a portion thereof. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for about 2 years, about 3 years, or any period in between. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for about 2 to about 3 years (e.g., about 2 years, about 2.5 years, about 3 years). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for less than about 2 years (e.g., about 1.5 years or less, about 1 year or less, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for more than about 3 years (e.g., about 3.5 years or more, about 4 years or more, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once every 2 weeks for only a portion of the active/inflammatory phase of Graves' ophthalmopathy (e.g., half or a majority of the active/inflammatory phase). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks until sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence of one or more symptoms of Grave's ophthalmopathy. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks as a single subcutaneous injection. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once every 2 weeks as two or more consecutive subcutaneous injections.

In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once monthly. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once

monthly for at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, at least 30 months, at least 36 months, or longer. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for the entire active/inflammatory phase of Graves' ophthalmopathy, or a portion thereof. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for about 2 years, about 3 years, or any period in between. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for about 2 to about 3 years (e.g., about 2 years, about 2.5 years, about 3 years). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for less than about 2 years (e.g., about 1.5 years or less, about 1 year or less, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for more than about 3 years (e.g., about 3.5 years or more, about 4 years or more, etc.). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered once monthly for only a portion of the active/inflammatory phase of Graves' ophthalmopathy (e.g., half or a majority of the active/inflammatory phase). In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once monthly until sufficient to treat, prevent, reduce the severity, delay the onset, and/or reduce the risk of occurrence of one or more symptoms of Grave's ophthalmopathy. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once monthly as a single subcutaneous injection. In some embodiments, the antibody, antigen-binding fragment, or pharmaceutical composition is administered to the patient once monthly as two or more consecutive subcutaneous injections.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the therapeutically effective amount of the antibody or antigen-binding fragment is about 200 to 300 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 200 to 300 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 300 to 400 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 300 to 400 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 400 to 500 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 400 to 500 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 500 to 600 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 500 to 600 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 255 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 255 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 340 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 340 mg administered once weekly.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the therapeutically effective amount of the antibody or antigen-binding fragment is about 550 to 650 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 550 to 650 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 650 to 750 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 650 to 750 mg administered once weekly. In some

embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 750 to 850 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 750 to 850 mg administered once weekly. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 680 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is about 680 mg administered once weekly.

In some embodiments of the therapeutic methods, uses, and compositions disclosed herein, the therapeutically effective amount of the antibody or antigen-binding fragment is at least one dose of at least about 680 mg (i.e., about 680 mg or more), followed by at least one dose of about 340 mg. In some embodiments, the therapeutically effective amount of the antibody or antigen-binding fragment is 3 doses of at least about 680 mg per dose (i.e., about 680 mg or more per dose, e.g., 680 mg per dose), followed by 3 doses of about 340 mg per dose (e.g., 340 mg per dose).

In some embodiments, the at least one dose of at least about 680 mg is administered subcutaneously. In some embodiments, the at least one dose of at least about 680 mg is administered as two consecutive subcutaneous injections. In some embodiments, the at least one dose of at least about 680 mg is administered intravenously. In some embodiments, the at least one dose of at least about 680 mg comprises about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In some embodiments, the at least one dose of at least about 680 mg comprises about 3 doses.

In some embodiments, the at least one dose of about 340 mg is administered subcutaneously. In some embodiments, the at least one dose of about 340 mg is administered as one subcutaneous injection. In some embodiments, the at least one dose of about 340 mg comprises about one dose, about 2 doses, about 3 doses, about 4 doses, or about 5 doses. In some embodiments, the at least one dose of about 340 mg comprises about 3 doses.

In some embodiments, each dose of a multi-dose regimen (e.g., a multi-dose regimen described herein, e.g., at least one higher dose, followed by at least one lower dose) is administered once weekly. In some embodiments, each dose of a multi-dose regimen (e.g., a multi-dose regimen described herein, e.g., at least one higher dose, followed by at least one lower dose) is administered once every 2 weeks. In some embodiments, each dose of a multi-dose regimen (e.g., a multi-dose regimen described herein, e.g., at least one higher dose, followed by at least one lower dose) is administered once monthly.

In various embodiments, the present disclosure also provides a kit for use in the therapeutic applications described herein. In various embodiments, the present disclosure provides a kit comprising the anti-FcRn antibody or an antigen-binding fragment thereof for use in the treatment of prevention of Graves' ophthalmopathy. In various embodiments, the kit further comprises one or more additional components, including but not limited to: instructions for use; other agents, e.g., one or more additional therapeutic agents; devices, containers, or other materials for preparing the antibody or antigen-binding fragment for therapeutic administration; pharmaceutically acceptable carriers (e.g., excipients); and devices, containers, or other materials for administering the antibody or antigen-binding fragment to a patient. Instructions for use can include guidance for therapeutic applications including suggested dosages and/or modes of administration, e.g., in a patient having or suspected of having Grave's ophthalmopathy. In various embodiments, the kit comprises the anti-FcRn antibody or an antigen-binding fragment thereof and instructions for therapeutic use, e.g., the use of the antibody or antigen-binding fragment to treat or prevent Graves' ophthalmopathy in a patient. In various embodiments, the kit further contains at least one additional therapeutic agent (e.g., for administering in combination with the antibody or antigen-binding fragment). In various embodiments, the antibody or antigen-binding fragment is formulated as a pharmaceutical composition.

In some embodiments, the anti-FcRn antibody or antigen-binding fragment is produced by expression and purification using a gene recombination method. In some embodiments,

polynucleotide sequences that encode the variable regions of the antibody or antigen-binding fragment are produced by expression in separate host cells or simultaneously in a single host cell.

As used herein, the term "recombinant vector" refers to an expression vector capable of expressing a protein of interest in a suitable host cell. The term encompasses a DNA construct including essential regulatory elements operably linked to express a nucleic acid insert.

As used herein, the term "operably linked" refers to a nucleic acid expression control sequence functionally linked to a nucleic acid sequence encoding a protein of interest so as to execute general functions. Operable linkage with the recombinant vector can be performed using a gene recombination technique well known in the art, and site-specific DNA cleavage and ligation can be easily performed using enzymes generally known in the art.

A suitable expression vector may include expression regulatory elements such as a promoter, an operator, an initiation codon, a stop codon, a polyadenylation signal, and an enhancer, as well as a signal sequence for membrane targeting or secretion. The initiation and stop codons are generally considered as part of a nucleotide sequence encoding the immunogenic target protein, and are necessary to be functional in an individual to whom a genetic construct has been administered, and must be in frame with the coding sequence. Promoters may generally be constitutive or inducible. Prokaryotic promoters include, but are not limited to, lac, tac, T3 and T7 promoters. Eukaryotic promoters include, but are not limited to, simian virus 40 (SV40) promoter, mouse mammary tumor virus (MMTV) promoter, human immunodeficiency virus (HIV) promoter such as the HIV Long Terminal Repeat (LTR) promoter, moloney virus promoter, cytomegalovirus (CMV) promoter, epstein barr virus (EBV) promoter, rous sarcoma virus (RSV) promoter, as well as promoters from human genes such as human β-actin, human hemoglobin, human muscle creatine, and human metallothionein. The expression vector may include a selectable marker that allows selection of host cells containing the vector. Genes coding for products that confer selectable phenotypes, such as resistance to drugs, a nutrient requirement, or resistance to cytotoxic agents or expression of surface proteins, may be used as general selectable

markers. Since only cells expressing a selectable marker survive in the environment treated with a selective agent, transformed cells can be selected. Also, a replicable expression vector may include a replication origin, a specific nucleic acid sequence that initiates replication. Recombinant expression vectors that may be used include various vectors such as plasmids, viruses, and cosmids. The kind of recombinant vector is not limited, and the recombinant vector could function to express a desired gene and produce a desired protein in various host cells such as prokaryotic and eukaryotic cells. In some embodiments, a vector that can produce a large amount of a foreign protein similar to a natural protein while having strong expression ability with a promoter showing strong activity is used.

A variety of expression host/vector combinations may be used to express the anti-FcRn antibody or an antigen-binding fragment thereof. For example, expression vectors suitable for the eukaryotic host include, but are not limited to, SV40, bovine papillomavirus, adenovirus, adeno-associated virus, cytomegalovirus, and retrovirus. Expression vectors that may be used for bacterial hosts include bacterial plasmids such as pET, pRSET, pBluescript, pGEX2T, pUC, col E1, pCR1, pBR322, pMB9 and derivatives thereof, a plasmid such as RP4 having a wider host range, phage DNA represented as various phage lambda derivatives such as gt10, gt11 and NM989, and other DNA phages such as M13 and filamentous single-stranded DNA phage. Expression vectors useful in yeast cells include 2 μm plasmid and derivatives thereof. A vector useful in insect cells is pVL941.

In some embodiments, the recombinant vector is introduced into a host cell to form a transformant. Host cells suitable for use include prokaryotic cells such as E. coli, Bacillus subtilis, Streptomyces sp., Pseudomonas sp., Proteus mirabilis and Staphylococcus sp., fungi such as Aspergillus sp., yeasts such as Pichia pastoris, Saccharomyces cerevisiae, Schizosaccharomyces sp., and Neurospora crassa, and eukaryotic cells such as lower eukaryotic cells, and higher other eukaryotic cells such as insect cells.

In some embodiments, host cells are derived from plants or animals (e.g., mammals), and examples thereof include, but are not limited to, monkey kidney cells (COS7), NSO cells, SP2/0, Chinese hamster ovary (CHO) cells, W138, baby hamster kidney (BHK) cells, MDCK, myeloma cells, HuT 78 cells and HEK293 cells. In some embodiments, CHO cells are used.

Transfection or transformation into a host cell may include any method by which nucleic acids can be introduced into organisms, cells, tissues or organs, and, as known in the art, may be performed using a suitable standard technique selected according to the kind of host cell. Methods include, but are not limited to, electroporation, protoplast fusion, calcium phosphate ($CaPO_4$) precipitation, calcium chloride ($CaCl_2$) precipitation, agitation with silicon carbide fiber, and agrobacterium-, PEG-, dextran sulfate-, lipofectamine- and desiccation/inhibition-mediated transformation.

The anti-FcRn antibody or antigen-binding fragment can be produced in large amounts by culturing the transformant comprising the recombinant vector in nutrient medium, and the medium and culture conditions that are used can be selected depending on the kind of host cell. During culture, conditions, including temperature, the pH of medium, and culture time, can be controlled so as to be suitable for the growth of cells and the mass production of protein. The antibody or antigen-binding fragment produced by the recombination method as described herein can be collected from the medium or cell lysate and can be isolated and purified by conventional biochemical isolation techniques (Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press (1989); Deuscher, Guide to Protein Purification Methods Enzymology, Vol. 182. Academic Press. Inc., San Diego, CA (1990)). These techniques include, but are not limited to, electrophoresis, centrifugation, gel filtration, precipitation, dialysis, chromatography (e.g., ion exchange chromatography, affinity chromatography, immunosorbent chromatography, size exclusion chromatography, etc.), isoelectric point focusing, and various modifications and combinations thereof. In some embodiments, the antibody or antigen-binding fragment is isolated and purified using protein A.

EXAMPLES

Hereinafter, the present disclosure will be described in further detail with reference to examples. It will be obvious to a person having ordinary skill in the art that these examples are illustrative purposes only and are not to be construed to limit the scope of the present disclosure.

Example 1: Construction of anti-FcRn-expressing library using transgenic rats

Immunization was performed using a total of six transgenic rats (OmniRat®, OMT). As an immunogen, human FcRn was used. Both footpads of the rats were immunized eight times with 0.0075 mg of human FcRn (each time) together with an adjuvant at 3-day intervals for 24 days. On day 28, the rats were immunized with 5-10 μg of the immunogen diluted in PBS buffer. On day 28, rat serum was collected and used to measure the antibody titer. On day 31, the rats were euthanized, and the popliteal lymph node and the inguinal lymph node were recovered for fusion with P3X63/AG8.653 myeloma cells.

ELISA analysis was performed to measure the antibody titer in rat serum. Specifically, human FcRn was diluted in PBS (pH 6.0 or pH 7.4) buffer to make 2 μg/mL of a solution, and 100 μL of the solution was coated on each well of a 96-well plate, and then incubated at 4°C for at least 18 hours. Each well was washed three times with 300 μL of washing buffer (0.05% Tween 20 in PBS) to remove unbound human FcRn, and then 200 μL of blocking buffer was added to each well and incubated at room temperature for 2 hours. A test serum sample was diluted at 1/100, and then the solution was serially 2-fold diluted to make a total of 10 test samples having a dilution factor of 1/100 to 1/256,000). After blocking, each well was washed with 300 μL of washing buffer, and then each test sample was added to each cell and incubated at room temperature for 2 hours. After washing three times, 100 μL of a 1:50,000 dilution of secondary detection antibody in PBS buffer was added to each well and incubated at room temperature for 2 hours. After washing three times again, 100 μL of TMB solution was added to each well and

allowed to react at room temperature for 10 minutes, and then 50 μL of 1 M sulfuric acid-containing stop solution was added to each well to stop the reaction, after which the OD value at 450 nm was measured with a microplate reader. The anti-human FcRn (hFcRn) IgG titer resulting from immunization was higher than that in the pre-immune serum of the rats.

A total of three hybridoma libraries A, B and C fused using polyethylene glycol were made. Specifically, transgenic rats 1 and 5 were used to make hybridoma library A, and rats 2 and 6 were used to make hybridoma library B, and rats 3 and 4 were used to make hybridoma library C. A hybridoma library fusion mixture for constructing each hybridoma library was cultured in HAT-containing medium for 7 days so that only cells fused to HAT would be selected. Hybridoma cells viable in the HAT medium were collected and cultured in HT media for about 6 days, and then the supernatant was collected, and the amount of rat IgG in the supernatant was measured using a rat IgG ELISA kit (RD-biotech). Specifically, each sample was diluted at 1:100, and 100 μL of the dilution was added to each well of an ELISA plate and mixed with peroxidase-conjugated anti-rat IgG, followed by reaction at room temperature for 15 minutes. 100 μL of TMB solution was added to each well and allowed to react at room temperature for 10 minutes, and then 50 μL of 1 M sulfuric acid-containing stop solution was added to each well to stop the reaction. Next, the OD value at 450 nm was measured with a microplate reader.

Example 2: Evaluation of the antigen binding affinity and IgG binding blocking ability of anti-hFcRn antibodies of hybridoma libraries

To analyze the binding of antibodies to hFcRn, the same ELISA analysis (pH 6.0 and pH 7.4) as mentioned above was performed.

Using the culture supernatants of the three hybridoma libraries, the evaluation of the hFcRn binding affinity by FACS at 5 ng/mL and 25 ng/mL was performed at pH 6.0 and pH 7.4. Human FcRn-stable expressing HEK293 cells were detached from a flask, and then suspended in reaction buffer (0.05% BSA in PBS, pH 6.0 or pH 7.4). The suspension was diluted to a cell density

of 2 x 10^6 cells/mL, and 50 μL of the dilution was added to each well of a 96-well plate. Then, 50 μL of the hybridoma library culture supernatant diluted to each of 10 ng/mL and 50 ng/mL was added to each well and suspended to allow antibody to bind. A488 rabbit anti-IgG goat antibody was diluted at 1:200 in reaction buffer, and 100 μL of the dilution was added to each well and mixed with the cell pellets to perform a binding reaction, and then 150 μL of reaction buffer was added to each well. Measurement was performed in FACS (BD).

Evaluation of the human FcRn blocking ability of the hybridoma library by FACS was performed at pH 6.0. Specifically, naïve HEK293 cells and human FcRn-overexpressing HEK293 cells were suspended in reaction buffer (0.05% BSA in PBS, pH 6.0). 1 x 10^5 cells were added to a 96-well plate, and treated with each of 4 nM of each hybridoma library culture supernatant and 0.4 nM of a 10-fold dilution of the supernatant. To confirm the hIgG blocking ability, 100 nM A488-hIgG1 was added to each well, and then incubated on ice for 90 minutes. After completion of the reaction, the cell pellets were washed with 100 μL of reaction buffer, and transferred into a U-shaped round bottom tube, followed by measurement in FACS. The amount of 100 nM A488-hIgG1 remaining in the human FcRn-overexpressing stable cells was measured, and then the blocking (%) was calculated. As an isotype control, hIgG1 was used, and as a positive control, previously developed HL161-1Ag antibody was used to comparatively evaluate the antibody blocking effect. Each control was analyzed at concentrations of 1 μM and 2 μM, and the hybridoma library sample was measured at two concentrations of 0.4 nM and 4 nM.

Example 3: Isolation of hybridoma clone by FACS and selection of human antibodies

Using hybridoma library A showing the highest human FcRn binding affinity and blocking effect, clones were isolated by FACS (flow cytometry) to thereby obtain a total of 442 single clones. The isolated monoclones were cultured in HT media, and the supernatant was collected. Antibody-expressing hybridoma clones binding to hFcRn in the supernatant were selected by FACS.

RNA was isolated from 100 monoclones selected by FACS analysis and the isolated RNA was sequenced. In the first-step sequencing, 88 of the 100 monoclones were sequenced, and divided according to the amino acid sequence into a total of 35 groups (G1 to G38). The culture supernatants of the representative clones of 33 groups excluding two clones (G33 and G35) whose media were not available were diluted at a concentration of 100 ng/mL, and the binding affinity for hFcRn was evaluated by ELISA.

In the same manner as described above, evaluation of the hFcRn binding affinity by FACS was performed at pH 6.0 and 7.4. The order of the binding affinity of the clones was similar between the pHs, and the binding intensity appeared at various levels.

In addition, evaluation of the hFcRn blocking effects of the 33 clones was performed by FACS at pH 6.0. The blocking (%) was calculated based on the measured MFI value. Based on the results of analysis of the blocking % at a concentration of 1667 pM, the clones were divided into a total of the following four groups: group A: 70-100%; group B: 30-70%; group C: 10-30%; and group D: 10% or less.

For kinetic analysis of the hybridoma clones by SPR, human FcRn was immobilized, and then the analysis was performed using the hybridoma culture as an analyte.

Among the five hybridoma clones, the genes of 18 clones having no N-glycosylation site or free cysteine in the CDR sequences of groups A and B divided according to the results of analysis of the hFcRn blocking effect were converted to whole human IgG sequences.

Specifically, the amino acid sequence similarity between the VH and VL of the 18 selected antibodies and the human germ line antibody group was examined using the Ig BLAST program of the NCBI webpage.

In order to clone the 18 human antibody genes, restriction enzyme recognition sites were inserted into both ends of the genes in the following manner. EcoRI/ApaI were inserted into the heavy chain variable domain (VH); EcoRI/XhoI were inserted into the light chain lambda variable domain (VL(λ)); EcoRI/NheI restriction enzyme recognitions sites were inserted into the light

chain kappa variable domain (VL(κ)). In the case of the light chain variable domain, the light chain lambda variable (VL(λ)) gene sequence was linked to the human light chain constant (LC(λ)) region gene during gene cloning, and the light chain kappa variable (VL(κ)) gene sequence was linked to the human light chain constant (LC(κ)) region gene.

In cloning into pCHO1.0 expression vectors for expression of antibodies in animal cells, the light chain and heavy chain genes were inserted after cleavage with EcoRV, PacI, AvrII and BstZ17I restriction enzymes. In order to examine whether pCHO1.0 expression vectors containing the 18 selected human antibody genes were consistent with the synthesized gene sequences, DNA sequencing was performed.

Using the pCHO1.0 expression vectors that are animal cell expression systems containing all the antibody light chain and heavy chain genes, whole human IgG was expressed. The human antibody was obtained by transiently transfecting the plasmid DNA of each of the antibodies into CHO-S cells and purifying the antibody, secreted into the medium, by protein A column.

Human IgG was injected into hFcRn-expressing Tg32 (hFcRn+/+, hβ2m+/+, mFcRn-/-, mβ2m-/-) mice (Jackson Laboratory), and then the 18 human antibodies converted to the human IgG sequences were administered to the mice in order to examine whether the antibodies would influence the catabolism of human IgG.

Based on the *in vitro* analysis results for binding affinity (K_D) for the antigen and the analysis of human FcRn binding affinity and blocking effect by FACS, and the *in vivo* analysis of catabolism of human IgG, four human anti-FcRn antibody proteins (HL161A, HL161B, HL161C and HL161D) were selected (**FIG. 1**). In addition, an HL161BK antibody having no N-glycosylation site was prepared by substituting the asparagine (N) at position 83 of the heavy chain variable domain of the HL161B antibody with lysine (K). An HL161BKN antibody (RVT-1401) was also prepared by substituting the lysines (K) at positions 238 and 239 of the heavy chain (i.e., within the IgG1 heavy chain constant region) of the HL161BK antibody with alanines (A). Nucleotide sequences, amino acid sequences and CDR sequences of selected human FcRn

antibodies are shown in Tables 1-5.

Table 1. Polynucleotide sequences of heavy chain and light chain variable domains of selected human FcRn antibodies

Antibody name	Heavy chain variable domain sequence		Light chain variable domain sequence	
	SEQ ID NO.	Polynucleotide sequence	SEQ ID NO.	Polynucleotide sequence
HL161A	1	GAAGTGCAGC TGCTGGAATC CGGCGGAGGC CTGGTGCAGC CTGGCGGCTC TCTGAGACTG TCCTGCGCCG CCTCCGAGTT CACCTTCGGC AGCTGCGTGA TGACCTGGGT CCGACAGGCT CCCGGCAAGG GCCTGGAATG GGTGTCCGTG ATCTCCGGCT CCGGCGGCTC CACCTACTAC GCCGACTCTG TGAAGGGCCG GTTCACCATC TCCCGGGACA ACTCCAAGAA CACCCTGTAC CTGCAGATGA ACTCCCTGCG GGCCGAGGAC ACCGCCGTGT ACTACTGCGC CAAGACCCCC TGGTGGCTGC GGTCCCCCTT CTTCGATTAC TGGGGCCAGG GCACCCTGGT GACAGTGTCC TCC	11	TCTTACGTGC TGACCCAGCC CCCCTCCGTG TCTGTGGCTC CTGGCCAGAC CGCCAGAATC ACCTGTGGCG GCAACAACAT CGGCTCCACC TCCGTGCACT GGTATCAGCA GAAGCCCGGC CAGGCCCCCG TGCTGGTGGT GCACGACGAC TCCGACCGGC CTTCTGGCAT CCCTGAGCGG TTCTCCGGCT CCAACTCCGG CAACACCGCC ACCCTGACCA TCTCCAGAGT GGAAGCCGGC GACGAGGCCG ACTACTACTG CCAAGTGCGA GACTCCTCCT CCGACCACGT GATCTTCGGC GGAGGCACCA AGCTGACCGT GCTGGGCCAG CCTAAGGCCG CTCCCTCCGT GACCCTG

HL161B	3	CAACTGTTGC TCCAGGAATC CGGTCCTGGT CTTGTAAAGC CATCTGAGAC TCTCTCCCTT ACCTGTACCG TTAGCGGAGG AAGTCTTTCC TCAAGCTTCT CCTACTGGGT GTGGATCAGA CAGCCTCCCG GAAAAGGGTT GGAGTGGATT GGCACAATAT ACTACTCCGG CAACACTTAC TATAACCCCA GCCTGAAGAG CAGGCTGACT ATCTCTGTCG ACACCAGTAA AAATCACTTT TCTCTGAATC TGTCTTCAGT GACCGCAGCC GACACCGCCG TGTATTATTG CGCTCGGCGC GCCGGGATTC TGACAGGCTA TCTGGATTCA TGGGGCCAGG GGACATTGGT TACAGTGTCT AGT	13	TCTTACGTGC TGACCCAGTC CCCCTCCGTG TCCGTGGCTC CTGGCCAGAC CGCCAGAATC ACCTGTGGCG GCAACAACAT CGGCTCCAAG TCCGTGCACT GGTATCAGCA GAAGCCCGGC CAGGCCCCCG TGCTGGTGGT GTACGACGAC TCCGACCGGC CCTCTGGCAT CCCTGAGCGG TTCTCCGCCT CCAACTCCGG CAACACCGCC ACCCTGACCA TCTCCAGAGT GGAAGCCGGC GACGAGGCCG ACTACTACTG CCAAGTGTGG GACTCCTCCT CCGACCACGT GGTGTTCGGC GGAGGCACCA AGCTGACCGT GCTGGGCCAG CCTAAGGCCG CTCCCTCCGT GACCCTG
HL161BK (HL161BKN)	5	CAGCTGCTGC TGCAAGAATC CGGCCCTGGC CTGGTGAAAC CCTCCGAGAC ACTGTCCCTG ACCTGCACCG TGTCCGGCGG CTCCCTGTCC TCCAGCTTCT CCTACTGGGT CTGGATCCGG CAGCCCCCTG GCAAGGGCCT GGAATGGATC GGCACCATCT	15	TCTTACGTGC TGACCCAGTC CCCCTCCGTG TCCGTGGCTC CTGGCCAGAC CGCCAGAATC ACCTGTGGCG GCAACAACAT CGGCTCCAAG TCCGTGCACT GGTATCAGCA GAAGCCCGGC CAGGCCCCCG TGCTGGTGGT GTACGACGAC TCCGACCGGC

		ACTACTCCGG CAACACCTAC TACAACCCCA GCCTGAAGTC CCGGCTGACC ATCTCCGTGG ACACCTCCAA GAACCACTTC AGCCTGAAGC TGTCCTCCGT GACCGCCGCT GACACCGCCG TGTACTACTG TGCCAGAAGG GCCGGCATCC TGACCGGCTA CCTGGACTCT TGGGGCCAGG GCACCCTGGT GACAGTGTCC TCC		CCTCTGGCAT CCCTGAGCGG TTCTCCGCCT CCAACTCCGG CAACACCGCC ACCCTGACCA TCTCCAGAGT GGAAGCCGGC GACGAGGCCG ACTACTACTG CCAAGTGTGG GACTCCTCCT CCGACCACGT GGTGTTCGGC GGAGGCACCA AGCTGACCGT GCTGGGCCAG CCTAAGGCCG CTCCCTCCGT GACCCTG
HL161C	7	CAGGTGCAGC TCGTGCAGTC CGGCGCAGAG GTCAAAAAGC CTGGTGCATC TGTGAAAGTG AGTTGCAAGG CTAGCGGCTA CACCTTTACC GGATGTTATA TGCATTGGGT ACGCCAAGCC CCCGGACAAG GCTTGGAATG GATGGGGCGT ATCAACCCAA ACTCTGGCGG GACTAATTAC GCCCAGAAGT TTCAGGGAAG GGTGACTATG ACAAGGGACA CATCCATATC CACCGCTTAT ATGGACCTGT CTCGACTGCG GTCTGATGAT ACAGCCGTTT ATTACTGCGC CAGAGACTAC AGCGGATGGA GCTTCGATTA	17	GACATCCAGA TGACCCAGTC ACCATCATCC CTTTCCGCAT CTGTCGGAGA TAGAGTGACT ATCACCTGCA GGGCTTCTCA AGGTATTTCC AACTACCTCG CCTGGTTCCA GCAAAAGCCA GGTAAAGCCC CAAAGAGCTT GATCTACGCC GCTTCTAGTC TGCAGAGTGG AGTTCCTAGT AAGTTCTCCG GCTCTGGCAG TGGCACAGAT TTTACCTTGA CCATTTCCAG CCTGCAGTCT GAGGATTTCG CTACCTACTA TTGTCAGCAG TATGACAGCT ATCCCCCCAC ATTTGGGGGG GGCACTAAGG TGGAGATAAA

		TTGGGGGCAG GGTACTTTGG TCACAGTTTC AAGT		ACGGACAGTG GCTGCCCCTT CTGTCTTTAT T
HL161D	9	CAGCTGCAGT TGCAGGAGTC AGGCCCCGGT TTGGTTAAGC CTTCTGAAAC CCTTTCTCTC ACATGCACAG TATCCGGTGG CTCCATCTCC AGTTCAAGTT ACTACTGGGG ATGGATCCGG CAACCCCCAG GAAAAGGGCT GGAGTGGATT GGCAATATAT ATTACTCTGG GTCCACCTAT TACAACCCTT CCCTGATGAG TAGAGTGACC ATCAGCGTGG ACACAAGCAA AAACCAATTC AGCCTGAAGC TTTCTAGCGT GACCGCTGCC GACACAGCTG TCTATTACTG TGCCCGCCAG CTTAGTTATA ACTGGAATGA TAGGCTGTTT GATTACTGGG GCCAGGGGAC TCTCGTTACA GTCAGCAGC	19	AGCTATGAGC TGACCCAGCC TCTGAGCGTA TCTGTCGCTC TCGGCCAGAC AGCCAGAATT ACCTGTGGCG GCAATAACAT AGGATCCAAA AATGTTCACT GGTATCAGCA AAAACCTGGC CAAGCTCCCG TGCTCGTGAT CTACCGGGAC TCTAACCGAC CCAGTGGAAT CCCCGAACGC TTTAGCGGTT CCAACTCTGG AAATACAGCT ACTCTGACTA TCTCCAGGGC TCAGGCCGGG GATGAGGCCG ATTACTACTG CCAGGTGTGG GACTCAAGCA CAGTGGTCTT CGGCGGAGGT ACCAAGTTGA CTGTTCTTGG GCAGCCAAAG GCCGCACCTT CAGTGACCCT G

Table 2. Amino acid sequences of heavy chain and light chain variable domains of selected human FcRn antibodies

Antibody name	Heavy chain variable domain sequence		Light chain variable domain sequence	
	SEQ ID NO.	Amino acid sequence	SEQ ID NO.	Amino acid sequence
HL161A	2	EVQLLESGGG LVQPGGSLRL SCAASEFTFG SCVMTWVRQA PGKGLEWVSV ISGSGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKTP WWLRSPFFDY WGQGTLVTVSS	12	SYVLTQPPSV SVAPGQTARI TCGGNNIGST SVHWYQQKPG QAPVLVVHDD SDRPSGIPER FSGSNSGNTA TLTISRVEAG DEADYYCQVR DSSSDHVIFG GGTKLTVLGQ PKAAPSVTL
HL161B	4	QLLLQESGPG LVKPSETLSL TCTVSGGSLS SSFSYWVWIR QPPGKGLEWI GTIYYSGNTY YNPSLKSRLT ISVDTSKNHF SLNLSSVTAA DTAVYYCARR AGILTGYLDS WGQGTLVTVSS	14	SYVLTQSPSV SVAPGQTARI TCGGNNIGSK SVHWYQQKPG QAPVLVVYDD SDRPSGIPER FSASNSGNTA TLTISRVEAG DEADYYCQVW DSSSDHVVFG GGTKLTVLGQ PKAAPSVTL
HL161BK (HL161BKN)	6	QLLLQESGPG LVKPSETLSL TCTVSGGSLS SSFSYWVWIR QPPGKGLEWI GTIYYSGNTY YNPSLKSRLT ISVDTSKNHF SLKLSSVTAA DTAVYYCARR AGILTGYLDS WGQGTLVTVSS	16	SYVLTQSPSV SVAPGQTARI TCGGNNIGSK SVHWYQQKPG QAPVLVVYDD SDRPSGIPER FSASNSGNTA TLTISRVEAG DEADYYCQVW DSSSDHVVFG GGTKLTVLGQ PKAAPSVTL

HL161C	8	QVQLVQSGAE VKKPGASVKV SCKASGYTFT GCYMHWVRQA PGQGLEWMGR INPNSGGTNY AQKFQGRVTM TRDTSISTAY MDLSRLRSDD TAVYYCARDY SGWSFDYWGQ GTLVTVSS	18	DIQMTQSPSS LSASVGDRVT ITCRASQGIS NYLAWFQQKP GKAPKSLIYA ASSLQSGVPS KFSGSGSGTD FTLTISSLQS EDFATYYCQQ YDSYPPTFGG GTKVEIKRTV AAPSVFI
HL161D	10	QLQLQESGPG LVKPSETLSL TCTVSGGSIS SSSYYWGWIR QPPGKGLEWI GNIYYSGSTY YNPSLMSRVT ISVDTSKNQF SLKLSSVTAA DTAVYYCARQ LSYNWNDRLF DYWGQGTLVT VSS	20	SYELTQPLSV SVALGQTARI TCGGNNIGSK NVHWYQQKPG QAPVLVIYRD SNRPSGIPER FSGSNSGNTA TLTISRAQAG DEADYYCQVW DSSTVVFGGG TKLTVLGQPK AAPSVTL

Table 3. Polynucleotide sequences of full-length heavy chain and light chain of selected human FcRn antibodies

Antibody name	Heavy chain sequence		Light chain sequence	
	SEQ ID NO.	Polynucleotide sequence	SEQ ID NO.	Polynucleotide sequence
HL161BKN	45	CAG CTG CTG CTG CAA GAA TCC GGC CCT GGC CTG GTG AAA CCC TCC GAG ACA CTG TCC CTG ACC TGC ACC GTG TCC GGC GGC TCC CTG TCC TCC AGC TTC TCC TAC TGG GTC TGG ATC CGG CAG CCC CCT GGC AAG GGC CTG GAA TGG ATC GGC ACC ATC TAC TAC TCC GGC AAC ACC TAC TAC AAC CCC AGC CTG AAG TCC CGG CTG ACC ATC TCC GTG GAC ACC TCC AAG AAC CAC TTC AGC CTG AAG CTG TCC TCC GTG ACC GCC GCT GAC ACC GCC GTG TAC TAC TGT GCC AGA AGG GCC GGC ATC CTG ACC GGC TAC CTG GAC TCT TGG GGC CAG GGC ACC CTG GTG ACA GTG TCC TCC GCC TCC ACC AAG	47	TCT TAC GTG CTG ACC CAG TCC CCC TCC GTG TCC GTG GCT CCT GGC CAG ACC GCC AGA ATC ACC TGT GGC GGC AAC AAC ATC GGC TCC AAG TCC GTG CAC TGG TAT CAG CAG AAG CCC GGC CAG GCC CCC GTG CTG GTG GTG TAC GAC GAC TCC GAC CGG CCC TCT GGC ATC CCT GAG CGG TTC TCC GCC TCC AAC TCC GGC AAC ACC GCC ACC CTG ACC ATC TCC AGA GTG GAA GCC GGC GAC GAG GCC GAC TAC TAC TGC CAA GTG TGG GAC TCC TCC TCC GAC CAC GTG GTG TTC GGC GGA GGC ACC AAG CTG ACC GTG CTG GGC CAG CCT AAG GCC GCT CCC TCC GTG ACC CTG TTC CCC CCA TCC TCC GAG

		GGC CCC TCC GTG TTC		GAA CTG CAG GCC AAC
		CCT CTG GCC CCC TCC		AAG GCC ACC CTG GTC
		AGC AAG TCC ACC TCT		TGC CTG ATC TCC GAC
		GGC GGC ACC GCT GCC		TTC TAC CCT GGC GCC
		CTG GGC TGT CTG GTG		GTG ACC GTG GCC TGG
		AAA GAC TAC TTC CCC		AAG GCC GAC AGC TCT
		GAG CCC GTG ACC GTG		CCT GTG AAG GCC GGC
		TCC TGG AAC TCT GGC		GTG GAA ACC ACC ACC
		GCC CTG ACC TCC GGC		CCC TCC AAG CAG TCC
		GTG CAC ACC TTC CCT		AAC AAC AAA TAC GCC
		GCC GTG CTG CAG TCC		GCC TCC TCC TAC CTG
		TCC GGC CTG TAC TCC		TCC CTG ACC CCC GAG
		CTG TCC AGC GTG GTG		CAG TGG AAG TCC CAC
		ACC GTG CCC TCC AGC		CGG TCC TAC AGC TGC
		TCT CTG GGC ACC CAG		CAA GTG ACA CAC GAG
		ACC TAC ATC TGC AAC		GGC TCC ACC GTG GAA
		GTG AAC CAC AAG CCC		AAG ACC GTG GCC CCT
		TCC AAC ACC AAG GTG		ACC GAG TGC TCC
		GAC AAG CGG GTG GAA		
		CCC AAG TCC TGC GAC		
		AAG ACC CAC ACC TGT		
		CCC CCC TGT CCT GCC		
		CCT GAA GCT GCT GGC		
		GGC CCT AGC GTG TTC		
		CTG TTC CCC CCA AAG		
		CCC AAG GAC ACC CTG		
		ATG ATC TCC CGG ACC		
		CCC GAA GTG ACC TGC		
		GTG GTG GTG GAC GTG		
		TCC CAC GAG GAC CCT		
		GAA GTG AAG TTC AAT		

		TGG TAC GTG GAC GGC GTG GAA GTG CAC AAC GCC AAG ACC AAG CCC AGA GAG GAA CAG TAC AAC TCC ACC TAC CGG GTG GTG TCC GTG CTG ACC GTG CTG CAC CAG GAC TGG CTG AAC GGC AAA GAG TAC AAG TGC AAG GTC TCC AAC AAG GCC CTG CCT GCC CCC ATC GAA AAG ACC ATC TCC AAG GCC AAG GGC CAG CCC CGC GAG CCC CAG GTG TAC ACA CTG CCC CCT AGC CGG GAA GAG ATG ACC AAG AAC CAG GTG TCC CTG ACA TGC CTG GTG AAG GGC TTC TAC CCC TCC GAC ATT GCC GTG GAA TGG GAG TCC AAC GGC CAG CCC GAG AAC AAC TAC AAG ACC ACC CCC CCT GTG CTG GAC TCC GAC GGC TCA TTC TTC CTG TAC TCC AAG CTG ACC GTG GAC AAG TCC CGG TGG CAG CAG GGC AAC GTG TTC TCC TGC TCC GTG ATG CAC GAG GCC		

		CTG CAC AAC CAC TAC ACC CAG AAG TCC CTG TCC CTG AGC CCC GGC		

Table 4. Amino acid sequences of full-length heavy chain and light chain of selected human FcRn antibodies

Antibody name	Heavy chain sequence		Light chain sequence	
	SEQ ID NO.	Amino acid sequence	SEQ ID NO.	Amino acid sequence
HL161BKN	46	QLLLQESGPG LVKPSETLSL TCTVSGGSLS SSFSYWVWIR QPPGKGLEWI GTIYYSGNTY YNPSLKSRLT ISVDTSKNHF SLKLSSVTAA DTAVYYCARR AGILTGYLDS WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEAAG GPSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG	48	SYVLTQSPSV SVAPGQTARI TCGGNNIGSK SVHWYQQKPG QAPVLVVYDD SDRPSGIPER FSASNSGNTA TLTISRVEAG DEADYYCQVW DSSSDHVVFG GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE GSTVEKTVAP TECS

Table 5. CDR sequences of heavy chain and light chain variable domains of selected human FcRn antibodies

Antibody	Heavy chain variable domain CDR			Light chain variable domain CDR		
	CDR1	CDR2	CDR3	CDR1	CDR2	CDR3
SEQ ID NO.	21	22	23	24	25	26
HL161A	SCVMT	VISGSGGSTYYADSVKG	TPWWLRSPFFDY	GGNNIGSTSVH	DDSDRPS	VRDSSSDHVI
SEQ ID NO.	27	28	29	30	31	32
HL161B (HL161BK) (HL161BKN)	FSYWV	TIYYSGNTYYNPSLKS	RAGILTGYLDS	GGNNIGSKSVH	DDSDRPS	QVWDSSSDHVV
SEQ ID NO.	33	34	35	36	37	38
HL161C	GCYMH	RINPNSGGTNYAQKFQG	DYSGWSFDY	RASQGISNYLA	AASSLQS	QQYDSYPPTF
SEQ ID NO.	39	40	41	42	43	44
HL161D	SYYWG	NIYYSGSTYYNPSLMS	QLSYNWNDRLFDY	GGNNIGSKNVH	RDSNRPS	QVWDSSTVV

Example 4: Measurement of antigen binding affinity of HL161A, HL161B, HL161C, and HL161D antibodies by surface plasmon resonance (SPR)

The binding affinities of HL161A, HL161B, HL161C and HL161D antibodies were measured by SPR by immobilizing water-soluble hFcRn as a ligand onto a Proteon GLC chip (Bio-Rad) and measuring the affinity. Kinetic analysis was performed using a Proteon XPR36 system. Water-soluble human FcRn (shFcRn) was immobilized on a GLC chip, and an antibody sample was allowed to react at a concentration of 5, and sensogram results were obtained. In kinetic analysis, a 1:1 Langmuir binding model was used, the analysis was repeated six times at each of pH 6.0 and pH 7.4, and the mean K_D value was calculated. Following the immobilization step, the chip was activated under the conditions of EDAC/NHS 0.5X, 30 μL/min and 300 seconds. For immobilization, shFcRn was diluted in acetate buffer (pH 5.5) to concentrations of 2 μg/mL and 250 μL, and the dilution was allowed to flow on the chip at a rate of 30 μL/min. When an immobilization level of 200-300 RU was reached, the reaction was stopped. Then, deactivation was performed using ethanolamine at a rate of 30 μL/min for 300 seconds. Each of the HL161 antibodies was serially 2-fold diluted from a concentration of 10 nM to 5 nM, 2.5 nM, 1.25 nM, 0.625 nM, 0.312 nM, etc., thereby preparing samples. Sample dilution was performed using 1X PBST (pH 7.4) or 1X PBST (pH 6.0) at each pH. For sample analysis, association was performed at 50 μL/min for 200 seconds, and the dissociation step was performed at 50 μL/min for 600 seconds, after which regeneration was performed using glycine buffer (pH 2.5) at 100 μL/min for 18 seconds. The kinetic analysis of each sample was repeated six times, and then the mean antigen binding affinity (K_D) was measured. The kinetic parameters of the antibodies, which resulted from the SPR analysis, are shown in Table 6 (**FIG. 2A** to **FIG. 2H**).

Table 6. Results of kinetic analysis of antibody by human FcRn-immobilized SPR

Antibody	pH 6.0			pH 7.4		
	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)	k_{on} ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	K_D (M)
HL161A	1.81×10^{6}	3.26×10^{-4}	1.80×10^{-10}	1.32×10^{6}	3.27×10^{-4}	2.47×10^{-10}
HL161B	9.12×10^{5}	7.35×10^{-4}	8.07×10^{-10}	7.10×10^{5}	1.25×10^{-3}	1.76×10^{-9}
HL161C	1.74×10^{6}	3.32×10^{-4}	1.91×10^{-10}	1.36×10^{6}	3.16×10^{-4}	2.32×10^{-10}
HL161D	9.70×10^{5}	1.38×10^{-3}	1.43×10^{-9}	6.99×10^{5}	1.24×10^{-3}	1.78×10^{-9}
$hIgG_1$	3.2×10^{5}	4.6×10^{-4}	1.4×10^{-9}	No binding	No binding	No binding

Example 5: Analysis of binding of HL161A and HL161B antibodies to human FcRn by FACS

Using human FcRn-expressing stable HEK293 cells, binding to FcRn at each pH was analyzed using a FACS system. The FcRn binding test using FACS was performed in reaction buffer at pH 6.0 and pH 7.4. Specifically, 100,000 human FcRn-expressing stable HEK293 cells were washed with PBS buffer and centrifuged in a table microcentrifuge at 4500 rpm for 5 minutes to obtain cell pellets. The antibody was added to 100 µL of pH 6.0 or pH 7.4 PBS/10 mM EDTA. The remaining cell pellets were suspended in reaction buffer, and cell counting was performed. 10 µL of the cell suspension was added to a slide, and the number of the cells in the cell suspension was counted in a TC10 system, after which the cell suspension was diluted with reaction buffer to a cell concentration of 2 x 10^6 cells/mL. Each antibody sample was diluted to 500 nM. For analysis at pH 6.0, the dilution was diluted to 20 nM in a 96-well v-bottom plate, and 50 µL of the dilution was added to each well. For analysis at pH 7.4, 500 nM antibody sample was diluted by 3-fold serial dilution, and analyzed at a concentration ranging from 250 nM to 0.11 nM. 50 µL of the cells diluted to 2 x 10^6 cells/mL were added to each well and suspended. The plate was mounted in a rotator at 4°C and rotated at an angle of 15° and 10 rpm for 90 minutes. After

completion of the reaction, the plate was taken out of the rotator and centrifuged at 2000 rpm for 10 minutes, and the supernatant was removed. A488 anti-hIgG goat antibody was diluted at 1:200 in reaction buffer, and 100 μL of the antibody dilution was added to each well and suspended. Next, the plate was mounted again in a rotator at 4°C and rotated at an angle of 15° and 10 rpm for 90 minutes. After completion of the reaction, the plate was taken out of the rotator and centrifuged at 2000 rpm for 10 minutes, and the supernatant was removed. After the washing procedure was performed once more, 100 μL of reaction buffer was added to each well to dissolve the cell pellets, and the plate was transferred into a blue test tube. Next, 200 μL of reaction buffer was added to each well, and then measurement was performed in FACS. The FACS measurement was performed under the following conditions: FS 108 volts, SS 426 volts, FL1 324 volts, FL2 300 volts. These cells were analyzed by FACS using BD FACSDiva™ v6.1.3 software (BD Bioscience). The results were expressed as Mean Fluorescence Intensity (MFI) (**FIG. 3**). The HL161A and HL161B antibodies showed MFI values of 10.59 and 8.34, respectively, at a concentration of 10 nM and pH 6.0. At pH 7.4 and a concentration of 0.11-250 nM, the antibodies showed EC50 (Effective Concentration 50%) values of 2.46 nM and 1.20 nM, respectively, as analyzed by 4 parameter logistic regression using the MFI values.

Example 6: Analysis of blocking effects of HL161A and HL161B antibodies by FACS

HEK293 cells that express hFcRn on the cell surface were treated with the HL161A and HL161B antibodies (previously analyzed for their binding affinity for cell surface human FcRn), and the blocking effects of the antibodies were examined based on a reduction in the binding of Alexa-Fluo-488-labeled hIgG1. The analysis procedure was performed in the following manner:

2 mL of 1 x TE was added to each type of naïve HEK293 cells and human FcRn-overexpressing stable HEK293 cells, which were incubated in a 5% CO_2 incubator at 37°C for 1 minute. The cells were recovered from the flasks, and 8 mL of reaction buffer (pH 6.0) was added thereto, after which the cells were transferred into a 50 mL conical tube. The cell

suspension was centrifuged at 2000 rpm for 5 minutes to remove the supernatant, and 1 mL of reaction buffer (pH 6.0) was added to each cell pellet. Then, the cell suspension was transferred into a fresh 1.5 mL Eppendorf tube. Next, the cell suspension was centrifuged at 4000 rpm for 5 minutes, and the supernatant was removed. Then, reaction buffer (pH 6.0) was added to the remaining cell pellet, and the cell number of the cell suspension was counted. Finally, the cell suspension was diluted with reaction buffer to a cell concentration of 2.5×10^6 cells/mL.

Each antibody sample was diluted to 400 nM, and then diluted by 4-fold serial dilution in a 96-well v-bottom plate. 50 µL of the sample diluted to a final concentration of 200 nM to 0.01 nM was added to each well. Then, 10 µL of Alex488-hIgG1 diluted with 1 µM reaction buffer (pH 6.0) was each well. Finally, 40 µL of cells diluted to a cell concentration of 2.5×10^6 cells/mL were added to each well and suspended. The plate was mounted in a rotator at 4°C and rotated at an angle of 15° and 10 rpm for 90 minutes. After completion of the reaction, the plate was taken out of the rotator, and centrifuged at 2000 rpm for 10 minutes to remove the supernatant. 100 µL of reaction buffer was added to each well to dissolve the cell pellets, and the plate was transferred into a blue test tube. Then, 200 µL of reaction buffer was added to each well, and measurement was performed in FACS. The FACS measurement was performed under the following conditions: FS 108 volts, SS 426 volts, FL1 324 volts, FL2 300 volts. These cells were analyzed by FACS using BD FACSDiva™ v6.1.3 software (BD Bioscience). The results were expressed as mean fluorescence intensity (MFI). The MFI of the test group was processed after subtracting the measured MFI value of the cells alone (background signal). The percentage of the MFI of the competitor-containing tube relative to 100% of a control tube (Alexa Fluor 488 alone, and no competitor) was calculated.

$$\text{Blocking}(\%) = \left\{ \frac{\text{MFI of hFcRn stable (Competitor+ A488-hIgG1)} - \text{MFI of HEK293 (A488-hIgG1)}}{\text{MFI of hFcRn stable (A488-hIgG1)} - \text{MFI of HEK293 (A488-hIgG1)}} \right\} \times 100$$

When the MFI was lower than the MFI of the human IgG1 competitor-containing tube, the competitor antibody was determined to have high competition rate. Based on the measured blocking effects (%) of the HL161A and HL161B antibodies under the conditions of pH 6.0 and concentration of 0.01-200 nM, 4-parameter logistic regression was performed. As a result, it was shown that the HL161A and HL161B antibodies showed IC50 (Inhibitory Concentration 50%) values of 0.92 nM and 2.24 nM, respectively (**FIG. 4**).

Example 7: Test for effects of HL161A and HL161B in mFcRn -/- hFCRN transgenic 32 (Tg32) mice

Human IgG was injected into human FcRn-expressing Tg32 (hFcRn+/+, hβ2m+/+, mFcRn-/-, mβ2m-/-) mice (Jackson Laboratory), and then HL161A and HL161B together with human IgG were administered to the mice in order to examine whether the antibodies would influence the catabolism of human IgG.

HL161A and HL161B antibodies and human IgG (Greencross, IVglobulinS) were dispensed for 4-day administration at dose of 5, 10 and 20 mg/kg and stored, and PBS (phosphate buffered saline) buffer (pH 7.4) was used as a vehicle and a 20 mg/kg IgG1 control. Human FcRn Tg32 mice were adapted for about 7 days and given water and feed *ad libitum*. Temperature (23 ± 2 °C), humidity (55 ± 5%) and 12-hr-light/12-hr-dark cycles were automatically controlled. Each animal group consisted of 4 mice. To use human IgG as a tracer, biotin-conjugated hIgG was prepared using a kit (Pierce, Cat#. 21327). At 0 hour, 5 mg/kg of biotin-hIgG and 495 mg/kg of human IgG were administered intraperitoneally to saturate IgG *in vivo*. At 24, 48, 72 and 96 hours after administration of biotin-IgG, each drug was injected intraperitoneally at doses of 5, 10 and 20 mg/kg once a day. For blood collection, the mice were lightly anesthetized with Isoflurane (JW Pharmaceutical), and then blood was collected from the retro-orbital plexus using a heparinized Micro-hematocrit capillary tube (Fisher) at 24, 48, 72, 96, 120 and 168 hours after

administration of biotin-IgG. At 24, 48, 72 and 96 hours, the drug was administered after blood collection. Immediately after 0.1 mL of whole blood was received in an Eppendorf tube, plasma was separated by centrifugation and stored in a deep freezer (Thermo) at -70°C until analysis.

The level of biotin-hIgG1 in the collected blood was analyzed by ELISA in the following manner. 100 μL of Neutravidin (Pierce, 31000) was added to a 96-well plate (Costar, Cat. No: 2592) to a concentration of 1.0 μg/mL, and then coated at 4°C for 16 hours. The plate was washed three times with buffer A (0.05 % Tween-20, 10 mM PBS, pH 7.4), and then incubated in 1% BSA-containing PBS (pH 7.4) buffer at room temperature for 2 hours. Next, the plate was washed three times with buffer A, and then a Neutravidin plate was prepared with 0.5 % BSA-containing PBS (pH 7.4) buffer so as to correspond to 1 μg/mL. A blood sample was serially diluted 500-1000-fold in buffer B (100 mM MES, 150 mM NaCl, 0.5 % BSA IgG-free, 0.05 % Tween-20, pH 6.0), and 150 μL of the dilution was added to each well of the plate. The added sample was allowed to react at room temperature for 1 hour. Next, the plate was washed three times with buffer A, and then 200 μL of 1 nM HRP-conjugated anti-human IgG goat antibody was added to each well and incubated at 37°C for 2 hours. Next, the plate was washed three times with ice cold buffer B, and then 100 μL of the substrate solution tetramethylbenzidine (RnD, Cat. No: DY999) was added to each well and allowed to react at room temperature for 15 minutes. 50 μL of 1.0 M sulfuric acid solution (Samchun, Cat. No: S2129) was added to each well to stop the reaction, after which the absorbance at 450 nm was measured.

The concentration of biotin-IgG after 24 hours (approximately Tmax of biotin-IgG in mice; before the occurrence of catabolism of biotin-IgG) was set at 100%, and the percentages of the concentration at other time points relative to the concentration at 24 hours were analyzed. The half-lives of the vehicle and the 20 mg/kg IgG1 control were 103 hours and 118 hours, respectively. The IgG half-lives of the HL161A antibody were 30, 23, and 18 hours at varying doses. In addition, the HL161B antibody showed IgG half-lives of 41, 22, and 21 hours (**FIG. 5A** and **FIG. 5B**).

Example 8: Test for effects of HL161A and HL161B in monkeys

Using cynomolgus monkeys having a homology of 96% to human FcRn, the monkey IgG, IgA, IgM and albumin levels by administration of the HL161A and HL161B antibodies were analyzed, and the pharmacokinetics (PK) profiles of the antibodies were analyzed.

1) Analysis of change in expression of immunoglobulin G in monkey blood

First, a change in monkey IgG was measured by ELISA analysis. 100 μL of anti-human IgG Fc antibody (BethylLab, A80-104A) was loaded into each well of a 96-well plate (Costar, Cat. No: 2592) to a concentration of 4.0 μg/mL, and then coated at 4°C for 16 hours. The plate was washed three times with washing buffer (0.05% Tween-20, 10 mM PBS, pH 7.4), and then incubated with 1% BSA-containing PBS (pH 7.4) buffer at room temperature for 2 hours. The standard monkey IgG was used at a concentration of 3.9-500 ng/mL, and the blood sample was diluted 80,000-fold in 1% BSA-containing PBS (pH 7.4) buffer, and the dilution was loaded into the plate and incubated at room temperature for 2 hours. Next, the plate was washed three times with washing buffer, and then 100 μL of a 20,000-fold dilution of anti-hIgG antibody (Biorad, 201005) was loaded into the plate and allowed to react at room temperature for 1 hour. After each plate was washed, 100 μL of the substrate solution 3,3',5,5'- tetramethylbenzidine (RnD, Cat. No: DY999) was loaded into the plate and allowed to react at room temperature for 7 minutes, after which 50 μL of 1.0 M sulfuric acid solution (Samchun, Cat. No: S2129) was added to each well to stop the reaction. For analysis, absorbance (OD) was measured using a 450 nm and 540 nm absorbance reader (MD, Model: VersaMax). Change (%) in monkey IgG level by administration of the HL161A and HL161B antibodies is shown in Table 7 and **FIG. 6A** to **FIG. 6C**.

Table 7. Change (%) in monkey IgG level by administration of HL161A and HL161B

Day	Vehicle	HL161A		HL161B	
		5 mg/kg	20 mg/kg	5 mg/kg	20 mg/kg
0 day	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0
0.5 day	99.0±4.8	81.5±1.8	101.5±9.0	94.3±5.4	96.2±3.0
1 day	97.6±15.9	67.2±2.0	86.2±11.9	83.9±24.7	94.1±7.0
2 day	97.8±6.2	63.0±3.3	74.2±14	73.7±11.3	71.7±5.4
3 day	104.5±13.1	61.8±8.0	59.2±11.0	68.3±9.3	61.3±6.0
4 day	100.9±16.7	55.3±4.1	45.1±4.6	65.5±12.2	44.3±5.6
5 day	103.4±12.5	60.8±8.3	38.8±4.9	65.0±11.9	38.4±3.7
6 day	113.3±8.5	64.9±11.7	39.7±6.4	66.4±11.3	39.0±5.4
7 day	116.9±23.3	58.7±4.7	39.6±5.4	61.4±8.0	37.5±3.2
7.5 day	92.4±10.4	51.2±7.2	38.7±7.8	62.8±8.3	39.3±0.4
8 day	94.6±8.7	48.0±9.3	36.1±5.3	60.7±7.5	39.6±5.9
9 day	117.6±14.3	47.1±4.4	33.8±5.0	54.3±6.9	31.0±3.1
10 day	115.1±16.7	49.7±8.9	29.6±5.8	53.6±4.9	32.8±4.3
11 day	114.6±18.9	47.7±4.2	30.4±6.5	54.7±4.2	39.9±9.1
12 day	109.5±13.1	51.7±3.1	32.9±5.7	56.5±4.7	46.7±9.1
13 day	111.1±21.2	52.9±6.4	35.7±9.2	58.7±3.8	45.4±7.6
14 day	128.9±17.7	54.7±4.2	37.8±9.6	60.6±4.2	53.8±11.3
17 day	95.6±6.6	59.5±10.3	40.2±7.4	56.7±4.4	48.4±10.0
20 day	92.5±8.4	62.4±6.7	47.6±8.9	61.8±6.0	54.0±9.5
23 day	107.1±15.2	71.9±6.5	61.8±13.3	64.9±4.4	56.8±6.0
26 day	104.0±5.6	77.7±6.8	72.2±22.4	70.8±7.4	62.4±5.8
29 day	102.4±8.3	81.4±6.7	77.9±20.5	74.8±5.1	65.4±10.8

2) Analysis of pharmacokinetic profiles of HL161A and HL161B in monkey blood

The time-dependent pharmacokinetic profiles (PK) of HL161A and HL161B after intravenous administration were analyzed by competitive ELISA. Specifically, a solution of 2 μg/mL of Neutravidin was prepared, and 100 μL of the solution was coated on each well of a 96-well plate, and then incubated at 4°C for 18 hours. The plate was washed three time with 300 μL of wash buffer (0.05% Tween 20 containing 10 mM PBS, pH 7.4), and then each well was incubated with 1% BSA-containing PBS (pH 7.4) buffer at 25°C for 2 hours. Biotinylated hFcRn was diluted with PBS to 1 μg/mL, and then 100 μL of the dilution was added to each well of the 96-well plate and incubated at 25°C for 1 hour. Next, the plate was washed three times with 300 μL of wash buffer to remove unbound hFcRn, and then a standard sample (0.156-20 ng/mL) was added to each well and incubated at 25°C for 2 hours. Next, the plate was washed three times with wash buffer, and 100 μL of a 1:10,000 dilution of detection antibody in PBS was added to each well and incubated at 25°C for 1.5 hours. The plate was finally washed three times, and 100 μL of TMB solution was added to each buffer and incubated at room temperature for 5 minutes, after which 50 μL of 1 M sulfuric acid as a reaction stop solution was added to each well to stop the reaction. Next, the absorbance at 450 nm was measured with a microplate reader. The analysis results for pharmacokinetic profiles of HL161A and HL161B at varying doses are shown in Table 8, and (**FIG. 7A** and **FIG. 7B**).

Table 8. Analysis results for pharmacokinetic profiles of HL161A and HL161B at varying doses

Ab (Dose)	Day	Cmax (mg/ml)	AUC (mg/ml.hr)	$T_{1/2}$ (hr)
HL161A (5 mg/kg)	0-7	157 ± 31	1,601 ± 501	6.9 ± 0.9
	7-14	157 ± 25	1,388 ± 334	10.3 ± 2.8
HL161A (20 mg/kg)	0-7	692 ± 138	13,947 ± 2,459	9.0 ± 0.6
	7-14	724 ± 125	12,699 ± 2,114	7.6 ± 1.6

HL161B (5 mg/kg)	0-7	178 ± 56	2,551 ± 1,356	7.9 ± 1.3
	7-14	187 ± 9	2,772 ± 466	9.4 ± 0.5
HL161B (20 mg/kg)	0-7	823 ± 38	21,867 ± 1,088	11.7 ± 1.0
	7-14	868 ± 66	16,116 ± 1,501	6.8 ± 0.9

3) Analysis of change in IgM and IgA antibody levels in monkey blood

ELISA analysis for measuring IgM and IgA levels in monkey blood was performed in a manner similar to the ELISA method for measuring IgG levels. Specifically, 100 μL of anti-monkey IgM antibody (Alpha Diagnostic, 70033) or IgA antibody (Alpha Diagnostic, 70043) was added to each well of a 96-well plate to a concentration of 2.0 μg/mL, and then coated at 4°C for 16 hours. The plate was washed three times with wash buffer (0.05% Tween-20 containing 10 mM PBS, pH 7.4), and then incubated with 1% BSA-containing PBS (pH 7.4) buffer at room temperature for 2 hours. The standard monkey IgM was analyzed at a concentration of 7.8-1,000 ng/mL, and IgA was analyzed at 15.6-2,000 ng/mL. The blood sample was diluted 10,000- or 20,000-fold in 1% BSA-containing PBS (pH 7.4) buffer, and the dilution was added to each well and incubated at room temperature for 2 hours. Next, the plate was washed three times with wash buffer, and then 100 μL of a 5,000-fold dilution of each of anti-monkey IgM secondary antibody (Alpha Diagnostic, 70031) and anti-monkey IgA secondary antibody (KPL, 074-11-011) was added to each well and allowed to react at room temperature for 1 hour. The plate was finally washed three times, and 100 μL of the substrate solution 3,3',5,5'-tetramethylbenzidine (RnD, Cat. No: DY999) was added to each well and allowed to react at room temperature for 7 minutes. Next, 50 μL of 1.0 M sulfur solution (Samchun, Cat. No: S2129) was added to each well to stop the reaction. The absorbance of each well was measured with a 450 and 540 nm absorbance reader (MD, Model: VersaMax).

4) Analysis of change in albumin levels in monkey blood

The analysis of a change in albumin levels in monkey blood was performed using a commercial ELISA kit (Assaypro, Cat. No: EKA2201-1). Briefly, monkey serum as a test sample was 4000-fold diluted, and 25 μL of the dilution was added to each well of a 96-well plate coated with an antibody capable of binding to monkey albumin. 25 μL of biotinylated monkey albumin solution was added to each well and incubated at 25°C for 2 hours. The plate was washed three times with 200 μL of wash buffer, and then 50 μL of a 1:100 dilution of streptavidin-peroxidase conjugated antibody was added to each well and incubated at 25°C for 30 minutes. The plate was finally washed three times, and then 50 μL of a substrate was added to each well and incubated at room temperature for 10 minutes. Next, 50 μL of a reaction stop solution was added to each well, and the absorbance at 450 nm was measured. Change (%) in monkey IgM, IgA and albumin levels by administration of the HL161A and HL161B is shown in **FIG. 8A** to **FIG. 8C**.

5) Analysis of blood biochemical levels and urinary components

Finally, blood biochemical analysis and urinary analysis by administration of the antibodies were performed using samples on day 14 of the test. Blood biochemical markers, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinase (CPK), total bilirubin (TBIL), glucose (GLU), total cholesterol (TCHO), triglyceride (TG), total protein (TP), albumin (Alb), albumin/globulin (A/G), blood urea nitrogen (BUN), creatinine (CRE), inorganic phosphorus (IP), calcium (Ca), sodium (Na), potassium (K) and chloride (Cl), were analyzed using the Hitachi 7180 system. In addition, markers for urinary analysis, including leukocyte (LEU), nitrate (NIT), urobilinogen (URO), protein (PRO), pH, occult blood (BLO), specific gravity (SG), ketone body (KET), bilirubin (BIL), glucose (GLU), and ascorbic acid (ASC), were analyzed using the Mission U120 system. Measured levels were generally in the normal level ranges of cynomolgus monkeys.

Example 9: Open-label study of RVT-1401 for the treatment of patients with moderate to severe active Graves' ophthalmopathy

In an open-label, add-on-to-standard-of-care (SOC) study to assess the safety and tolerability of RVT-1401 in patients with moderate to severe active Graves' ophthalmopathy, patients diagnosed with moderate to severe active Graves' ophthalmopathy (GO) with evidence of anti-TSHR-IgG are treated with once weekly subcutaneous (SC) doses of RVT-1401 (680 mg for 2 weeks, followed by 340 mg for 4 weeks). The study design is shown in **FIG. 9** and outlined below.

Study Design:

Screening (3 to 6 Weeks) -

Patient are diagnosed and screened for main inclusion/exclusion criteria (Table 9).

Table 9. Main inclusion/exclusion criteria

	Criteria - Inclusion
1	Male or female ≥ 18 years of age
2	Clinical diagnosis of Graves' disease with hyperthyroidism associated with active, moderate to severe GO with a CAS ≥ 4 for the most severely affected eye at Screening (on the 7-item scale) and Baseline (on the 10-item scale).
3	Onset of active GO within 9 months of Screening.
4	Documented evidence at Screening of detectable auto-antibodies (anti-TSHR-IgG).
5	Does not require immediate surgical intervention and is not planning corrective surgery/irradiation or medical therapy for GO during the course of the study.
6	Moderate-to-severe active GO (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia.
7	Stable medical regimen; unlikely to require adjustment of medications during the 6-week treatment period.
8	Patients must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels < 50% above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the study.
9	Stable dose of allowed concomitant medications (e.g. antidepressants) for 3 months from Baseline.

10	Patients who are rendered euthyroid by the block-and-replace regimen (methimazole + adding thyroxine) when FT4 and T3 have become normal are allowed.
Criteria - Exclusion	
1	Use of oral and/or IV corticosteroid use for conditions other than GO within 3 weeks prior to Screening (topical steroids for dermatological conditions are allowed). These cannot be initiated during the study.
2	Use of any steroid (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone for the treatment of TED within 3 weeks prior to Screening.
3	Previous steroid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if the corticosteroid was discontinued at least 3 weeks prior to Screening.
4	Use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation within the past 9 months prior to Baseline.
5	Use of selenium 3 weeks prior to Baseline and use during the study (multivitamins that include selenium are allowed).
6	Use of biotin within 48 hours prior to any laboratory collection (this includes multivitamins that include biotin).
7	Patients with ≥ 2 pts (CAS) or 2 mm (proptosis) decrease between Screening and Baseline.
8	Total IgG level < 6 g/L at Screening.
9	Absolute neutrophil count <1500 cells/mm^3 at Screening.
10	Patients with decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months at Screening.
11	Previous orbital irradiation or surgery for GO.
12	Patient has any laboratory abnormality (at Screening) that is clinically significant, has not resolved at Baseline, and could jeopardize or would compromise the patient's ability to participate in the study.
13	Have known autoimmune disease other than GO that would interfere with the course and conduct of the study.
14	Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.
15	Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.
16	History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Patients must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®-TB Gold test at Screening. Patients with an indeterminate QuantiFERON®-TB Gold test result will be allowed one retest; if not negative on retesting, the patient will be excluded.
17	Patient has any clinically significant history of allergic conditions (including drug allergies, anaphylactic reactions) that would contraindicate his/her participation.

18	Patient has any medical condition (acute or chronic illness) or psychiatric condition that could jeopardize or would compromise the patient's ability to participate in the study.
19	Body Mass Index (BMI) at Screening ≥ 35 kg/m^2.
20	Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
21	Currently participating or has participated in another GO clinical study within 28 days prior to signing the informed consent form.
22	Patient has received a live vaccination within 8 weeks prior to the Baseline visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of study treatment.
23	Patient has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to Baseline.
24	History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that contraindicates participation.
25	Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at Screening or Baseline.
26	Patient has had their spleen removed.
27	QTcF interval >450 milliseconds for males and >470 milliseconds for females at Screening (a single repeat is allowed for eligibility determination). QTcF >480 msec in patients with Bundle Branch Block.

Treatment -

One group of approximately 8 patients (n=8) is administered via subcutaneous injection 680 mg of RVT-1401 once per week for 2 weeks, followed by 340 mg of RVT-1401 once per week for 4 additional weeks (Baseline to Week 6). Treatment is open-label and predicted to reduce anti-TSHR-IgG levels by approximately 40-80% by Week 7. During treatment, primary, secondary, and exploratory endpoints are assessed (Table 10). Reference therapies are beta-blockers and antithyroid drugs (e.g., methimazole). During and following treatment, primary, secondary, and exploratory endpoints are assessed up to Week 18 (Table 10).

Table 10. Primary, secondary, and exploratory endpoints

	Primary
1	Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from Baseline in vital signs, clinical laboratory values, and electrocardiograms
2	Change from Baseline in levels of anti-TSHR antibodies
3	Change from Baseline in levels of total IgG and IgG subclasses (I-IV)

Secondary	
1	Concentration of RVT-1401 pre-dose (Ctrough)
2	Immunogenicity determined by number of patients positive for anti-RVT-1401 antibodies and characterization of anti-RVT-1401 antibodies to confirm neutralization potential
3	Change from Baseline in proptosis
4	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye)
5	PK parameters of AUC (0-168 hours) and Cmax after first and last dose
Exploratory	
1	Change from Baseline in levels of anti-IGF-IR antibodies
2	Proportion of subjects with ≥2 point reduction in CAS (using a 7-point scale) AND ≥2 mm reduction in proptosis
3	Proportion of subjects with CAS of 0 or 1
4	Change from Baseline in CAS
5	Change from Baseline in the Gorman Score for diplopia
6	Change from Baseline in methimazole (or other anti-thyroid treatment) dose
7	Change from Baseline in the GO-QOL visual functioning and appearance subscale scores
8	Change from Baseline in CT-measured muscle volume, fat volume, total orbital volume, and proptosis
9	Change from Baseline in the levels of TSH, free T3, and free T4
10	Change from Baseline in the level of gene expression
11	Change from Baseline in the circulating level of pro-inflammatory cytokines/chemokines
12	FcRn receptor occupancy following RVT-1401 administration
13	Change from Baseline in ratios of stimulatory to total anti-TSHR and anti-IGF-1R antibodies
14	Change from Baseline in the levels of anti-TPO and anti-thyroglobulin antibodies
15	Proportion of patients with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye: (1) Reduction in proptosis by at least 2 mm; (2) Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); (3) Improvement in CAS by at least 2 points.

Example 10: Randomized, double-blind, placebo-controlled study of RVT-1401 for the treatment of patients with active, moderate to severe Graves' ophthalmopathy

In a randomized, double-blind, placebo-controlled, add-on-to-standard-of-care study to assess the efficacy and safety of RVT-1401 in patients with moderate to severe active Graves' ophthalmopathy, patients diagnosed with moderate to severe active Graves' ophthalmopathy with evidence of anti-TSHR-IgG are randomized (2:2:1:2) and treated with once weekly subcutaneous doses of RVT-1401 (680 mg), RVT-1401 (340 mg), RVT-1401 (255 mg), or placebo for 12 weeks. The study design is shown in **FIG. 10** and outlined below.

Study Design:

Screening (3 to 6 Weeks) -

Patient are diagnosed and screened for main inclusion/exclusion criteria (Table 11).

Table 11. Main inclusion/exclusion criteria

	Criteria - Inclusion
1	Male or female ≥ 18 years of age
2	Clinical diagnosis of Graves' disease with hyperthyroidism associated with active, moderate to severe GO with a CAS ≥ 4 for the most severely affected eye at Screening and Baseline.
3	Onset of active GO within 9 months of Screening.
4	Documented evidence at Screening of detectable anti-TSHR-IgG.
5	Does not require immediate surgical intervention and is not planning corrective surgery/irradiation or medical therapy for GO during the course of the study.
6	Moderate-to-severe active GO (not sight-threatening but has an appreciable impact on daily life), usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, proptosis ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia.
7	Stable medical regimen; unlikely to require adjustment of thyroid medications during the 12-week treatment period.
8	Patients must be euthyroid with the baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine [FT4] and free triiodothyronine [FT3] levels < 50% above or below the normal limits) at Screening. Every effort should be made to correct the mild hypo- or hyperthyroidism promptly and to maintain the euthyroid state for the full duration of the study.
9	Stable dose of allowed concomitant medications (e.g. antidepressants) for 3 months from Baseline.
10	Patients who are rendered euthyroid by the block-and-replace regimen (methimazole + adding thyroxine) when FT4 and T3 have become normal are allowed.

11	Patients who have received radioactive iodine treatment for Graves' hyperthyroidism >6 months from Screening are allowed.
Criteria - Exclusion	
1	Use of any steroid (IV, oral, steroid eye drops) for the treatment of GO or other conditions within 3 weeks prior to Screening (topical steroids for dermatological conditions are allowed). Steroids cannot be initiated during the study. Exceptions include topical and inhaled steroids, which are allowed.
2	Use of rituximab, tocilizumab, or any monoclonal antibody/Fc-fusion biologic for immunomodulation within the past 9 months prior to Baseline.
3	Use of selenium 3 weeks prior to Baseline and use during the study (multivitamins that include selenium are allowed).
4	Use of biotin within 48 hours prior to any laboratory collection (this includes multivitamins that include biotin).
5	Patients with ≥ 2 pts (CAS) or 2 mm (proptosis) decrease between Screening and Baseline.
6	Total IgG level < 6 g/L at Screening.
7	Absolute neutrophil count <1500 cells/mm^3 at Screening.
8	Albumin level <3.5 g/dL at Screening.
9	Known advanced liver disease including any diagnosis of cirrhosis of any stage. Non- alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH) is allowable if there has been a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.
10	AST or ALT ≥1.5x ULN at Screening. The participant may only be enrolled if s/he has a recent (within 6 months) normal ultrasound, CT, or MRI. If the ultrasound, CT, or MRI demonstrate fatty changes alone, the participant may be enrolled if s/he has a normal range fibroscan for liver fibrosis.
11	Patients with decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months at Screening.
12	Previous orbital irradiation or surgery for GO.
13	Patient has any laboratory abnormality (at Screening) that is clinically significant, has not resolved at Baseline, and could jeopardize or would compromise the patient's ability to participate in the study.
14	Have known autoimmune disease other than GO that would interfere with the course and conduct of the study.
15	Medical history of primary immunodeficiency, T-cell or humoral, including common variable immunodeficiency.
16	Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening.
17	History of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Mycobacterium tuberculosis. Patients must have negative

	test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®-TB Gold test at Screening. Patients with an indeterminate QuantiFERON®-TB Gold test result will be allowed one retest; if not negative on retesting, the patient will be excluded.
18	Hepatitis C virus (HCV): Participants must have a negative test result for HCV antibody OR Participants with a known history of HCV must have documented evidence of sustained virologic response that is consistent with cure of hepatitis C infection. This is defined as undetectable or unquantifiable HCV RNA at least 12 weeks after stopping HCV treatment (HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C; 2014-2018, AASLD and IDSA). This should be confirmed with a negative HCV RNA test at Screening.
19	Patient has any clinically significant history of allergic conditions (including drug allergies, anaphylactic reactions) that would contraindicate his/her participation.
20	Patient has any medical condition (acute or chronic illness) or psychiatric condition that could jeopardize or would compromise the patient's ability to participate in the study.
21	Body Mass Index (BMI) at Screening $\geq$ 35 kg/m^2.
22	Enrollment in a previous RVT-1401 clinical trial.
23	Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
24	Currently participating or has participated in another GO clinical study within 28 days prior to signing the informed consent form.
25	Patient has received a live vaccination within 8 weeks prior to the Baseline visit; or intends to have a live vaccination during the course of the study or within 7 weeks following the final dose of study treatment.
26	Patient has received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to Baseline and during the treatment period.
27	History of sensitivity to any of the study treatments, or components thereof or a history of drug or other allergy that contraindicates participation.
28	Pregnant or lactating females as determined by positive serum or urine human chorionic gonadotropin test at Screening or Baseline.
29	Patient has had their spleen removed.
30	QTcF interval >450 milliseconds for males and >470 milliseconds for females at Screening (a single repeat is allowed for eligibility determination). QTcF >480 msec in patients with Bundle Branch Block.

Treatment -

Approximately 77 patients are administered RVT-1401 via subcutaneous injection once per week. 22 patients are administered 680 mg per week for 12 weeks; 22 patients are administered 340 mg per week for 12 weeks; 11 patients are administered 255 mg per week for 12

weeks; and 22 patients are administered placebo for 12 weeks (Baseline to Week 12). Treatment is double-blind. Weekly doses of 680 mg, 340 mg, and 255 mg are predicted to reduce average total IgG levels by approximately 75-80%, 65-70%, and 45-55%, respectively, by the fourth or fifth dose. During and following treatment, primary, secondary, and exploratory endpoints are assessed up to Week 20 (Table 12).

Table 12. Primary, secondary, and exploratory endpoints

Primary	
1	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye)
2	Assessment of safety and tolerability by analysis of adverse event (AE) data and changes from Baseline in vital signs, clinical laboratory values, and electrocardiograms
Secondary	
1	Concentration of RVT-1401 pre-dose (Ctrough)
2	Immunogenicity determined by number of patients positive for anti-RVT-1401 antibodies and characterization of anti-RVT-1401 antibodies to confirm neutralization potential
3	Change from Baseline in proptosis
4	Proptosis responder rate (defined as percentage with ≥2 mm reduction in study eye without deterioration (≥2 mm increase) in fellow eye)
5	Change from Baseline in CAS
6	Proportion of subjects with CAS of 0 or 1
7	Proportion of patients with overall ophthalmic improvement defined as when at least two of the following outcome measures improves in one eye, without worsening in any of these measures in either eye: (1) Reduction in proptosis by at least 2 mm; (2) Improvement of ≥ 8 degrees in motility in any duction or improvement in diplopia (disappearance or change in degree); (3) Improvement in CAS by at least 2 points.
8	Change from Baseline in the Gorman Score for diplopia
9	Change from Baseline in the GO-QOL visual functioning and appearance subscale scores
10	Change from Baseline in levels of anti-TSHR antibodies
11	Change from Baseline in levels of total IgG and IgG subclasses (I-IV)
Exploratory	
1	Change from Baseline in levels of anti-IGF-IR antibodies
2	Change from Baseline in methimazole (or other anti-thyroid treatment) dose
3	Change from Baseline in CT-measured muscle volume, fat volume, total orbital volume, and proptosis
4	Change from Baseline in the levels of TSH, free T3, and free T4
5	Change from Baseline in the level of gene expression

6	Change from Baseline in the circulating level of pro-inflammatory cytokines/chemokines
7	Change from Baseline in ratios of stimulatory to total anti-TSHR and anti-IGF-1R antibodies
8	Change from Baseline in the levels of anti-TPO and anti-thyroglobulin antibodies

Although the present disclosure has been described in detail with reference to the specific features, it will be apparent to those skilled in the art that this description is only for purposes of illustration and does not limit the scope of the present disclosure. Thus, the substantial scope of the present disclosure will be defined by the appended claims and equivalents thereof.

CLAIMS

Claim 1. Use of an anti-FcRn antibody or an antigen-binding fragment thereof in the manufacture of a medicament for treating or preventing Thyroid Eye Disease in a patient in need thereof, wherein the medicament is suitable for administration to the patient comprises (i) a therapeutically effective amount of the antibody or antigen-binding fragment; or (ii) a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of the antibody or antigen-binding fragment, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 27 (HCDR1), an amino acid sequence of SEQ ID No: 28 (HCDR2), and an amino acid sequence of SEQ ID No: 29 (HCDR3); and a light chain variable region comprising an amino acid sequence of SEQ ID No: 30 (LCDR1), an amino acid sequence of SEQ ID No: 31 (LCDR2), and an amino acid sequence of SEQ ID No: 32 (LCDR3).

Claim 2. The use of claim 1, wherein the antibody or antigen-binding fragment comprises (i) a heavy chain variable region comprising an amino acid sequence of SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence of SEQ ID No: 16 or (ii) a heavy chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 6; and a light chain variable region comprising an amino acid sequence that is at least 90% identical to SEQ ID No: 16.

Claim 3. The use of claim 1 or claim 2, wherein the antibody or antigen-binding fragment binds to FcRn with a KD (dissociation constant) of 0.01 to 2 nM at pH 6.0 or pH 7.4.

Claim 4. The use of any one of claims 1 to 3, wherein the antibody, antigen-binding fragment, or

pharmaceutical composition is to be administered subcutaneously.

Claim 5. The use of any one of claims 1 to 4, wherein the antibody, antigen-binding fragment, or pharmaceutical composition is to be administered as a fixed dose.

Claim 6. The use of any one of claims 1 to 5, wherein the antibody, antigen-binding fragment, or pharmaceutical composition is to be administered once weekly or once every 2 weeks (bi-weekly).

Claim 7. The use of any one of claims 1 to 6, wherein the therapeutically effective amount of the antibody or antigen-binding fragment is:

a. 200 to 300 mg, 300 to 400 mg, 400 to 500 mg, or 500 to 600 mg to be administered once weekly;

b. 340 mg to be administered once weekly;

c. 550 to 650 mg, 650 to 750 mg, or 750 to 850 mg to be administered once weekly; and/or

d. 680 mg to be administered once weekly.

Claim 8. The use of any one of claims 1 to 7, wherein the therapeutically effective amount of the antibody or antigen-binding fragment is at least one dose of about 680 mg, followed by at least one dose of about 340 mg.

Claim 9. The use of claim 8, wherein the at least one dose of about 680 mg is to be administered subcutaneously or intravenously and/or wherein the at least one dose of about 340 mg is to be administered subcutaneously.

Claim 10. The use of claim 8, wherein the at least one dose of about 680 mg is 3 doses and/or wherein the at least one dose of about 340 mg is 3 doses.

Claim 11. The use of any one of claims 1 to 10, wherein the antibody, antigen-binding fragment, or pharmaceutical composition is to be administered alone or in combination with at least one additional therapeutic agent.

Claim 12. The use of any one of claims 1 to 11, wherein treatment reduces the level of at least one IgG in a sample from the patient.

Claim 13. The use of claim 12, wherein the at least one IgG comprises anti-TSHR IgG and/or anti-IGF-1R IgG.

Claim 14. The use of claim 13, wherein treatment reduces the level of anti-TSHR IgG and/or anti-IGF-1R IgG in a sample from the patient by at least 30%, 40%, 50%, 60%, 70%, or 80%.

Claim 15. The use of any one of claims 1 to 14, wherein treatment reduces the level of total serum IgG in a sample from the patient.

Claim 16. The use of claim 15, wherein treatment reduces the level of total serum IgG in a sample from the patient by at least 40%, 50%, 60%, 70%, or 80%.