METHODS AND COMPOSITIONS COMPRISING LONIGUTAMAB FOR TREATING TED

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 63/567,673, filed on March 20, 2024; U.S. Provisional Application No. 63/682,181, filed on August 12, 2024; and U.S. Provisional Application No. 63/727,078, filed on December 2, 2024; each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates to methods and treatments for certain conditions of the eye, such as Thyroid eye disease (TED).

BACKGROUND

[0003] Thyroid eye disease (TED), which is sometimes referred to as any one of thyroid-associated ophthalmopathy (TAO), Graves' ophthalmopathy or orbitopathy (GO), thyrotoxic exophthalmos, dysthyroid ophthalmopathy, and other appellations, is a complex, inflammatory disorder of the orbit. Thyroid eye disease (TED) may involve the orbital fibroblasts, adipocytes, extra-ocular muscles, optic nerve, and orbital vasculature, producing clinical presentations ranging from dry-eye to bilateral sight-threatening complications.

[0004] While the disease may have varying etiologies, the most common and well-researched etiology involves autoantibodies that activate the thyroid stimulating hormone receptor, which signals in conjunction with insulin-like growth factor-1 receptor (IGF-1R) to activate orbital fibroblasts. Fibroblast activation leads to secretion of hyaluronic acid and glycosaminoglycans, and cytokine production and recruitment, which together create an inflammatory milieu. Activated orbital fibroblasts also undergo rapid proliferation and differentiation into adipocytes, which deposit behind the eye, and myofibroblasts, which deposit within orbital muscle. Collectively, these deposits manifest by mechanically forcing the eye forward, resulting in proptosis of the eye, loss of muscle control, challenges with vision (including diplopia and strabismus), and can lead to blindness if left untreated. [1]

[0005] TED is a debilitating condition for those living with either acute or chronic forms of the disease. Over 100,000 people in the United States have TED, with approximately 35% of them experiencing a moderate-to-severe disease.

[0006] Approximately 25% of patients do not respond to treatment (proptosis response defined as ≥2 mm reduction in proptosis and diplopia response defined as improvement in ≥1 Bahn Gorman grade), even with newly approved therapies. There is a clear need for new treatment options that can improve and/or prolong responses. New treatments that are better tolerated and provide alternative dosing formulations (e.g., subcutaneous [SC] administration) could also be advantageous for patients. [1] There is an unmet need for development of therapies for treatment of TED with greater depth and durability of response. Additionally, the currently available therapies for treatment of TED have side-effects, including hearing impairment. These side-effects, which are reported in a substantial proportion of patients receiving currently available therapy, have limited treatment in patients with TED.

SUMMARY

[0007] In certain aspects, provided herein are pharmaceutical compositions comprising an anti-IGF-1R antibody, such as lonigutamab, as well as methods of using and making such pharmaceutical compositions for the treatment of TED. In certain embodiments, the pharmaceutical compositions of the invention are IGF-1R antibody solutions. In certain preferred embodiments, the IGF-1R antibody solutions comprise lonigutamab, or a fragment and/or derivative thereof. In certain embodiments, the pharmaceutical compositions provided herein comprise a high-concentration of lonigutamab antibody solution (e.g., such as higher than 20 mg/ml, or higher than 100 mg/ml, or higher than 250 mg/ml) while exhibiting a high agent stability and low viscosity.

[0008] In exemplary aspects, the IGF-1R antibody (e.g., lonigutamab) compositions are therefore amenable to subcutaneous delivery, including self-delivery, to patients suffering from thyroid eye disease, as well as other diseases and disorders for which anti-IGF-1R antibodies may provide a therapeutic benefit. Moreover, the high antibody concentration coupled with low viscosity of compositions provided herein allow for delivery to patients of lower volumes of composition through smaller needles, reducing patient discomfort and further facilitating self-delivery.

[0009] Lonigutamab is a humanized IgG1 monoclonal antibody targeting the IGF-1 receptor and is delivered subcutaneously. As disclosed herein, compositions and methods using lonigutamab, as first described herein, have demonstrated rapid improvements in proptosis and clinical activity score (CAS) at the first measurement – within three weeks after the first subcutaneous dose. Clinical results disclosed herein include the first reported clinical data for the anti-IGF-1R mechanism delivered subcutaneously, using lonigutamab, which demonstrates clinical benefit of the methods and compositions of the disclose in treating thyroid eye disease patients. The data demonstrate that compositions and methods using lonigutamab may optimize the benefit-to-risk of treating TED using the anti-IGF-1R mechanism by enabling longer-term subcutaneous dosing to increase depth and durability of clinical response while limit the safety liabilities seen with prior IV-treatments by minimizing exposures.

[0010] Relative to standard of care, lonigutamab binds to a distinct epitope, which results in internalization of the receptor within minutes, and in preclinical binding and functional laboratory assays, it has been shown to be 75-fold more potent. The characteristics of lonigutamab that enable subcutaneous delivery also enable the potential for longer-term dosing, which may improve depth and durability of clinical response compared to prior anti-IGF-1R treatments. The characteristics of lonigutamab also allow the potential to minimize exposures relative to IV therapy. IGF-1 is neuroprotective to cochlear cells of the inner ear and serves to repair damage that can occur over time. High concentrations of anti-IGF-1R treatment molecules due to C_{max} from IV administration can penetrate the blood-labyrinth barrier and interfere with this normal function. As disclosed herein, lonigutamab may be administered in subcutaneous doses with a frequency that optimizes its potential to improve depth and durability of response while minimizing safety risk.

[0011] In certain aspects, provided herein are methods of treating a disease or disorder comprising administering a pharmaceutical composition comprising lonigutamab. In some embodiments, the pharmaceutical composition is administered using an injector provided herein.

[0012] In preferred embodiments, the disease or disorder is thyroid eye disease (TED). In some embodiments, the disease or disorder is stroke, acromegaly, diabetic nephropathy (diabetic kidney disease), idiopathic pulmonary fibrosis, interstitial lung disease, obesity, type 2 diabetes, juvenile idiopathic arthritis (JIA), diffuse cutaneous systemic sclerosis, Sjogren's syndrome calcinosis and vasculitis, cachexia and sarcopenia, diabetic macular edema, arterial atherosclerosis, peripheral artery disease (PAD), myocardial infarction and stroke, diabetic foot and skin, rheumatoid arthritis,

neurofibromatosis 1, neurofibromatosis 2, polycystic kidney disease, polycystic liver disease, polycystic ovarian syndrome, Alzheimer's disease, cognitive decline, dementia, depression and anxiety, asthma, aging, thyroid eye disease, idiopathic orbital inflammation, human type 2 lipodystrophy and associated cardiomyopathy, autosomal dominant polycystic kidney disease (ADPKD), NASH, Graves' disease, and/or Hashimoto's thyroiditis.

[0013] In preferred embodiments, the disclosure provides methods for treating TED by administering to a subject with TED a pharmaceutical composition comprising lonigutamab for use in treating TED in the subject.

[0014] In preferred aspects, the disclosure provides methods of administration of pharmaceutical compositions comprising lonigutamab. These pharmaceutical compositions may be administered to patients suffering from thyroid eye disease (TED). In certain embodiments, the pharmaceutical compositions of the invention may be administered intravenously. The methods of the invention provide intravenous infusion of pharmaceutical compositions comprising between about 1.0 mg/kg lonigutamab and 5.0 mg/kg lonigutamab to the patient. In certain aspects, methods of the invention provide intravenous infusion of pharmaceutical compositions comprising between about 2.0 mg/kg lonigutamab and 4.0 mg/kg lonigutamab to the patient. In certain aspects, the methods of the invention provide intravenous infusion of pharmaceutical compositions comprising about 3.0 mg/kg lonigutamab to the patient.

[0015] In certain embodiments, methods of the invention provide administration of pharmaceutical compositions comprising about 0.1, 0.3, 0.5, 0.7, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0 or mg/kg of lonigutamab as an intravenous infusion. The invention further provides that the intravenous infusion may take place for a period of about 15 minutes to about 120 minutes. In certain preferred embodiments, the intravenous infusion takes place for a duration of about 60 minutes.

[0016] In certain aspects, the invention provides administration of pharmaceutical compositions comprising lonigutamab as a subcutaneous injection. In certain embodiments, the methods of the invention provide subcutaneous administration between about 10 mg and about 250 mg lonigutamab. In certain embodiments, the pharmaceutical composition for subcutaneous administration comprises about 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190

mg, 200 mg, 210 mg, 220 mg, 225 mg, 230 mg, 240 mg, 245 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or about 300 mg or more of lonigutamab. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises between about 20 mg and 80 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 40 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 50 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 60 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 70 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 80 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 90 mg. In certain aspects, the pharmaceutical composition for subcutaneous administration comprises about 40 mg to about 120 mg.

[0017] The pharmaceutical lonigutamab compositions for subcutaneous administration may have a volume of from about 0.1 mL to about 5 mL. In certain embodiments, the pharmaceutical compositions for subcutaneous administration may have a volume of from about 0.5 mL to about 3 mL. In preferred embodiments, the administered volume is about 1 mL.

[0018] Beneficially, since the subcutaneous administration is conducted within tolerable volumes, the pharmaceutical compositions could be administered in an out-patient setting, or the pharmaceutical compositions of the invention could be self-administered by the patients. This results in a convenient and an efficient way for administration of the pharmaceutical composition comprising lonigutamab. In particular, the subcutaneous administration of pharmaceutical compositions is beneficial as compared to the intravenous administration due to the ease of administration of the pharmaceutical composition.

[0019] Moreover, as demonstrated by pharmacokinetics, the subcutaneous administration of pharmaceutical compositions comprising lonigutamab results in an advantageous pharmacokinetic and pharmacodynamic characteristic of lonigutamab. Specifically, the subcutaneous administration of pharmaceutical compositions comprising lonigutamab results in a higher therapeutically effective serum concentration of lonigutamab for a longer duration.

[0020] In certain embodiments of the invention, the administration of pharmaceutical composition comprising lonigutamab results in maximal IGF-1R receptor occupancy with the anti-IGF-1R antibody.

[0021] This maximal occupancy of IGF-1R may be achieved any time after the administration of the pharmaceutical composition comprising lonigutamab. In certain embodiments, this is achieved after about 1 to 12 hours after administration of the pharmaceutical composition comprising lonigutamab. In certain embodiments, the pharmaceutical compositions administered may comprise from about 10 mg to about 500 mg lonigutamab. In certain embodiments, the pharmaceutical compositions administered may comprise from about 20 mg to about 400 mg lonigutamab. In preferred embodiments, the pharmaceutical compositions administered may comprise about 70 mg to about 300 mg lonigutamab. In preferred embodiments, the pharmaceutical compositions administered may comprise about 20 mg or about 40 mg or about 50 mg or about 70 mg lonigutamab. In preferred embodiments, the pharmaceutical composition may comprise about 125 mg or about 250 mg of lonigutamab. Notably, the maximal IGF-1R receptor occupancy may be maintained up to a few months after a single administration. In preferred embodiments, the IGF-1R receptor occupancy may be maintained for at least about 4 weeks after a single administration of a pharmaceutical composition comprising lonigutamab. The maximal receptor occupancy level may be maintained after a single subcutaneous injection or an intravenous infusion of pharmaceutical composition comprising lonigutamab.

[0022] In certain aspects, the serum concentration required for maximal IGF-1R receptor internalization is a concentration of at least about 0.1 μg/mL of lonigutamab. Thus, the therapeutically effective serum concentration of lonigutamab is at least about 0.1 μg/mL. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 1 μg/mL. Importantly, the pharmaceutical compositions of the invention provide a therapeutically effective serum concentration of lonigutamab to the patient. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 2 μg/mL. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 3 μg/mL.

[0023] In certain aspects of the invention, the pharmaceutical compositions comprising lonigutamab administered to the patients are safe and tolerable. Moreover, the pharmaceutical compositions of the invention have minimal adverse events.

[0024] In certain aspects, the invention provides methods of treatment of thyroid eye disease (TED) comprising subcutaneous administration of a pharmaceutical composition comprising from about 10 mg to about 500 mg lonigutamab. In certain embodiments, the pharmaceutical

composition comprises about 20 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 40 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 50 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 70 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 125 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 250 mg lonigutamab.

[0025] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered twice weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered thrice weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered on alternate days, *i.e.*, once every two days. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every two (2) weeks. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every three (3) weeks. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every four (4) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every five (5) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every six (6) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every eight (8) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every ten (10) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every twelve (12) weeks.

[0026] In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 14. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 21. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 28.

[0027] In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is subcutaneously administered at day 1 and day 14. In certain preferred embodiments, after a loading dose on day 1, the pharmaceutical composition comprising

lonigutamab is subcutaneously administered at day 14 and day 21. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is subcutaneously administered at day 1 and day 21. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is subcutaneously administered at day 1 and day 28.

[0028] In certain preferred embodiments, a pharmaceutical composition comprising about 100 mg lonigutamab is administered as a loading dose and subsequently, the pharmaceutical composition in an amount comprising about 50 mg lonigutamab or a similar pharmaceutical comprising about 50 mg lonigutamab is administered once every two weeks.

[0029] In certain aspects, provided herein is a pharmaceutical composition comprising: (a) at least 20 lonigutamab mg/ml of antibody; (b) from 20 to 30 mM histidine; and (c) from 4% to 6% of a sugar; wherein the pharmaceutical composition is in the pH range of 5.5-6.5. In some embodiments, the sugar is D-sorbitol.

[0030] In preferred aspects, the lonigutamab antibody comprises a CDRH1 of SEQ ID NO: 1, a CDRH2 of SEQ ID NO: 2, a CDRH3 of SEQ ID NO: 3, a CDRL1 of SEQ ID NO: 4, a CDRL2 of SEQ ID NO: 5, and a CDRL3 of SEQ ID NO: 6. In some embodiments, the antibody comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 7. In some embodiments, the antibody comprises a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 8. In certain embodiments, the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9. In some embodiments, the antibody comprises a light chain comprising an amino acid sequence of SEQ ID NO: 10. In some embodiments, the antibody comprises a heavy chain further comprising a charged amino acid at its c-terminus (e.g., a c-terminal arginine, histidine, lysine, aspartic acid, or glutamic acid). In some embodiments, the charged amino acid is a positively charged amino acid (e.g., arginine, histidine, or lysine). In some embodiments the charged amino acid is a negatively charged amino acid (e.g., aspartic acid, or glutamic acid). In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 11, 12, 13, 14, or 15. In some embodiments, the antibody comprises a human IgG1 heavy chain constant domain and a human kappa light chain constant domain.

[0031] Lonigutamab is a humanized monoclonal antibody against IGF-1R. Lonigutamab has high affinity and specificity toward IGF-1R. Specifically, lonigutamab has picomolar affinity for IGF-1R. In certain preferred embodiments, lonigutamab has a k_D of about 30 pM to a binding epitope

of IGF-1R. Once lonigutamab binds to IGF-1R, it induces receptor internalization, which results in signal blockade from IGF-1R, which may lead to the therapeutic effect of lonigutamab. The IGF-1R internalization may occur within minutes after administration of pharmaceutical compositions comprising lonigutamab. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab may be attained in about an hour after administration of the pharmaceutical composition comprising lonigutamab to a patient.

[0032] Lonigutamab has unique and beneficial pharmacological properties. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 70% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 80% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 85% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 90% IGF-1R internalization.

[0033] In some embodiments, the pharmaceutical composition comprises from 20 to 30 mM histidine. In certain embodiments, the pharmaceutical composition comprises about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, about 25 mM, about 26 mM, about 27 mM, about 28 mM, about 29 mM, or about 30 mM histidine.

[0034] In some embodiments, the pharmaceutical composition comprising lonigutamab comprises from 4% to 6% of a sugar (e.g., D-sorbitol). In certain embodiments, the pharmaceutical composition comprises about 4%, 5%, or 6% of a sugar (e.g., D-sorbitol).

[0035] In some embodiments, the pharmaceutical composition comprising lonigutamab is at a pH of from 5.5 to 6.5. In certain embodiments, the pharmaceutical composition is at a pH of about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, or about 6.5.

[0036] In some embodiments, the pharmaceutical composition comprising lonigutamab does not comprise polysorbate 80. In some embodiments, the pharmaceutical composition comprises a small amount of polysorbate 80 (e.g., less than 0.05%). In certain embodiments, the pharmaceutical composition comprises no more than 0.05% polysorbate 80. In some embodiments, the pharmaceutical composition comprises no more than 0.02% polysorbate 80. In some embodiments, the pharmaceutical composition comprising lonigutamab comprises no more

than 0.01% polysorbate 80. In some embodiments, the pharmaceutical composition comprises no more than 0.005% polysorbate 80. In certain embodiments, the pharmaceutical composition comprises from 0.002% to 0.05% polysorbate 80. In some embodiments, the pharmaceutical composition comprises about 0.002%, about 0.003%, about 0.004%, about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.015%, about 0.02%, about 0.025%, about 0.03%, about 0.035%, about 0.04%, about 0.045%, or about 0.05% polysorbate 80.

[0037] In some embodiments, the pharmaceutical composition comprising lonigutamab does not comprise poloxamer 188 (P188). In some embodiments, the pharmaceutical composition comprises a small amount of poloxamer 188 (e.g., less than 0.1%). In certain embodiments, the pharmaceutical composition comprises no more than 0.1% poloxamer 188. In some embodiments, the pharmaceutical composition comprises no more than 0.05% poloxamer 188. In some embodiments, the pharmaceutical composition comprises no more than 0.02% poloxamer 188. In some embodiments, the pharmaceutical composition comprises no more than 0.01% poloxamer 188. In some embodiments, the pharmaceutical composition further comprises from 0.01% to 0.1% poloxamer 188. In certain embodiments, the pharmaceutical composition comprises about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, or about 0.1% poloxamer 188.

[0038] In a preferred embodiment, the pharmaceutical composition comprises: (i) about 20-200 mg/ml lonigutamab; (ii) about 10-50 mM L-histidine; (iii) between 0% (w/v) and about 10% (w/v) sorbitol; and (iv) between 0% and about 0.1% polysorbate 80. In a preferred embodiment, the pharmaceutical composition comprises about 40-100 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises about 50 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises about 100 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises: (i) about 50 mg/ml lonigutamab; (ii) about 25 mM L-histidine; (iii) about 5% (w/v) sorbitol; and (iv) about 0.02% polysorbate 80 at pH 6.0. In a preferred embodiment, the pharmaceutical composition comprises: (i) about 100 mg/ml lonigutamab; (ii) about 25 mM L-histidine; (iii) about 5% (w/v) sorbitol; and (iv) about 0.02% polysorbate 80 at pH 6.0.

[0039] In certain embodiments, the osmolality of the pharmaceutical composition comprising lonigutamab is within physiological osmolality range of 250-400 mOsm/kg.

[0040] In certain embodiments, the viscosity of the pharmaceutical composition comprising lonigutamab is no more than 30 cP at 21°C. In certain embodiments, the viscosity of the pharmaceutical composition is no more than 15 cP at 21°C. In certain embodiments, the viscosity of the pharmaceutical composition is about 10 cP, about 11 cP, about 12 cP, about 13 cP, about 14 cP, about 15 cP, about 16 cP, about 17 cP, about 18 cP, about 19 cP, about 20 cP, about 21 cP, about 22 cP, about 23 cP, about 24 cP, about 25 cP, about 26 cP, about 27 cP, about 28 cP, about 29 cP, or about 30 cP at 21°C.

[0041] In certain embodiments, the pharmaceutical composition comprising lonigutamab is stable for at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks, at least 16 weeks, or longer. In some embodiments, the pharmaceutical composition is stable for such a length of time stable at a temperature of from -70°C to 8°C (e.g., at about -70°C, at about -20°C, at about 4°C).

[0042] In some aspects, provided herein is an injector or a syringe comprising the pharmaceutical composition comprising lonigutamab provided herein. In some embodiments, the injector comprises a delivery volume of no more than 2 ml (e.g., no more than 1.5 ml, no more than 1 ml). In some embodiments, the injector comprises a needle of a size of no bigger than 24G (e.g., 25G, 26G). In some embodiments, the injector comprises a needle of a size no bigger than 25G. In some embodiments, the injector comprises a needle of a size no bigger than 26G. In some embodiments, the injector comprises a needle of a size no bigger than 27G. In certain embodiments, the injector is an automatic reusable fix dose device. In some embodiments, the injector is an automatic reusable variable dose device. In some embodiments, the injector is an automatic disposable fix dose autoinjector.

[0043] In certain embodiments of the compositions and methods provided herein, the pharmaceutical composition comprising lonigutamab is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition is administered subcutaneously. In certain embodiments, the pharmaceutical composition comprising lonigutamab is formulated for intramuscular administration. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered intramuscularly. In some embodiments, the pharmaceutical composition comprising lonigutamab is formulated for infraorbital, intravitreal, intraocular, subconjunctival, retrobulbar, peribulbar, and/or intrathecal administration. In certain

embodiments, the pharmaceutical composition is administered by infraorbital, intravitreal, intraocular, subconjunctival, retrobulbar, peribulbar, and/or intrathecal injection.

[0044] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered in a delivery volume of no more than 3 ml, 2.5 ml, 2 ml, 1.5 ml, or 1 ml. In some embodiments, the pharmaceutical composition is administered in a delivery volume of no more than 2 ml.

[0045] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered via a needle of a size of no bigger than 24G, 25G, 26G, or 27G. In some embodiments, the pharmaceutical composition is administered in a 24G needle, a 25G needle, 26G needle, or a 27G needle.

[0046] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered with an injection force of no more than 14N, 13N, 12N, 11N, 10N, 9N, 8N, 7N, or 6N. In some embodiments, the pharmaceutical composition is administered with an injection force of no more than 12N. In certain embodiments, the pharmaceutical composition is administered with an injection force of about 4N, about 5N, about 6N, about 7N, about 8N, about 9N, about 10N, about 11N, or about 12N.

[0047] In certain embodiments, the method provided herein treats and/or prevents one or more disease or disorder by administration of a pharmaceutical composition comprising lonigutamab. In some embodiments, the disease or disorder is thyroid eye disease (TED). In certain embodiments, the method reduces the severity of the thyroid eye disease (TED). In the method reduces proptosis in an eye in a subject with thyroid eye disease (TED). In some embodiments, proptosis is reduced by at least 2 mm, at least 3 mm, or at least 4 mm.

[0048] In some embodiments, the method provided herein reduces Clinical Activity Score (CAS) of thyroid eye disease (TED). In some embodiments, the clinical activity score (CAS) is reduced by at least 2 points. In certain embodiments, the clinical activity score (CAS) is reduced to one (1). In certain embodiments, the clinical activity score (CAS) of the subject is reduced to zero (0).

[0049] In some embodiments, the method provided herein improves the European Group on Graves' Orbitopathy Clinical Activity Score (EUGOGO CAS) of the subject (e.g., by at least 1, 2, or 3). In certain embodiments, the method improves the patient's Clinical Measures of Severity Score (CMSS) (e.g., by at least 1, 2, or 3).

[0050] In certain embodiments, the method provided herein improves the quality of life in the subject. In some embodiments, the quality of life is measured by the Graves' Ophthalmopathy Quality of Life (GO-QoL) assessment. In certain embodiments, the quality of life is measured by the Visual Functioning or Appearance subscale thereof. In some embodiments, the quality of life is measured by the European Group on Graves' orbitopathy (EUGOGO) guidelines. In certain embodiments, the method provided herein reduces the severity of diplopia (e.g., constant diplopia, inconstant diplopia, intermittent diplopia).

[0051] In certain aspects, the present disclosure provides a long-lasting pharmaceutical composition comprising lonigutamab. In preferred aspects, the pharmaceutical composition comprising lonigutamab provides a therapeutically effective serum concentration of lonigutamab, an effective serum concentration of lonigutamab that is at least about 1-3μg/ml, and/or provides maximal IGF-1R receptor occupancy for at least about 4 weeks after a single administration of the pharmaceutical composition comprising lonigutamab. In preferred aspects, the present disclosure provides the long-lasting lonigutamab containing pharmaceutical composition for use in a patient suffering from TED and requiring amounts of delivered lonigutamab of about 10-500mg, particularly 20-300mg of lonigutamab per administration, wherein the long lasting lonigutamab containing pharmaceutical composition is administered subcutaneously to said patient in an amount of 10-500 mg, particularly 20-300 mg/administration and wherein the said pharmaceutical composition has a volume of 0.1 to 5 mL.

DESCRIPTION OF THE DRAWINGS

[0052] FIG. 1 shows data pertaining to adverse events after administration of pharmaceutical compositions comprising lonigutamab.

[0053] FIG. 2 shows serum concentrations of lonigutamab after intravenous infusion of 0.1, 0.3, 1.0, and 3.0 mg/kg lonigutamab.

[0054] FIG. 3 shows serum concentrations of lonigutamab after subcutaneous administration of 20 mg, 40 mg, 125 mg, and 250 mg lonigutamab.

[0055] FIG. 4 shows receptor occupancy-time profiles following intravenous infusion of 0.1, 0.3, 1.0, and 3.0 mg/kg lonigutamab.

[0056] FIG. 5 shows receptor occupancy-time profiles following subcutaneous administration of 20 mg, 40 mg, 125 mg, and 250 mg lonigutamab.

[0057] FIG. 6 shows the Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm for a phase 1/2 clinical trial of lonigutamab.

[0058] FIG. 7 shows an exemplary quality of life survey.

[0059] FIG. 8 outlines unique aspects of lonigutamab and its binding to IGF-1R.

[0060] FIG. 9A outlines a Phase 1/2 clinical trial evaluating lonigutamab in patients with TED.

[0061] FIG. 9B updates the Phase 1/2 clinical trial outlined in Fig. 9A with a third trial cohort after positive results in cohorts 1 and 2.

[0062] FIG. 10 outlines the demographics of Cohort 1 of the trial outlined in FIG. 9A.

[0063] FIG. 11A shows proptosis response data for Cohort 1.

[0064] FIG. 11B shows proptosis mean change during treatment period week 6 / off-treatment through week 12 for cohort 1.

[0065] FIG. 12 shows clinical activity score (CAS) responses for Cohort 1.

[0066] FIG. 13 shows CAS responses for Cohort 1.

[0067] FIG. 14 outlines the demographics of Cohort 2 of the trial outlined in FIG. 9A.

[0068] FIG. 15 provides proptosis and CAS responses for Cohort 2 and those of Cohort 1 at a comparable time.

[0069] FIG. 16A provides diplopia responses observed in Cohort 1 and Cohort 2 at week 6 compared with results for IV Teprotumumab IV.

[0070] FIG. 16B shows the diplopia response through week 12 for patients of cohort 1 with baseline diplopia >0.

[0071] FIGS. 17A-17B compare lonigutamab responses when administered subcutaneously with those of teprotumumab.

[0072] FIG. 18 summarizes safety data for Cohort 1 and Cohort 2.

[0073] FIG. 19 provides the results of GO-Quality of Life survey for cohort 1 starting from before treatment through the post-treatment period.

[0074] FIG. 20 provides proptosis responses for cohort 2 through week 12.

[0075] FIG. 21 provides proptosis mean change for cohort 2 through week 12.

[0076] FIG. 22 provides CAS mean changes and CAS individual changes for cohort 2 through week 12.

[0077] FIG. 23 provides the CAS of 0 or 1 through week 12 for cohort 2.

[0078] FIG. 24 provides the diplopia responses for cohort 2 through week 12.

[0079] FIG. 25 provides the results of GO-Quality of Life survey for cohort 2 starting from before treatment through the post-treatment period.

[0080] FIG. 26A-26B provide epitope availability data showing a clear dose/PK rand PD relationship in patients of cohort 1.

[0081] FIG. 27 outlines certain rationales for the doses used in cohorts 1-3.

[0082] FIG. 28 provides the demographics for the patients of cohort 3.

[0083] FIG. 29 provides the proptosis responses for cohort 3 through week 12.

[0084] FIG. 30 provides the proptosis mean change for cohort 3 through week 12.

[0085] FIG. 31 provides the CAS for cohort 3 through week 12.

[0086] FIG. 32 provides the CAS of 0 or 1 for cohort 3 through week 12.

[0087] FIG. 33 provides the diplopia responses trough week 12 for cohort 3.

[0088] FIG. 34 provides the GO-QOL overall score results for cohort 3 starting from before treatment through week 12.

[0089] FIG. 35 summarizes efficacy based on results from cohorts 1-3 and provides a comparison to results seen using teprotumumab ("tepro").

[0090] FIG. 36 summarizes efficacy responses for cohorts 1-3.

[0091] FIG. 37 summarizes the diplopia changes for cohorts 1-3 through week 12.

[0092] FIG. 38 outlines a summary of safety for cohorts 1-3.

[0093] FIG. 39 provides a summary of tinnitus events seen in cohorts 1-3.

[0094] FIGS. 40A-40H provide data associated with tinnitus in patients of cohorts 1-3.

[0095] FIG. 41 outlines the rationale for the dose chosen for cohort 4.

[0096] FIG. 42 provides a model showing lonigutamab concentrations and receptor occupancy (RO) for a 100 mg loading dose and 50 mg Q2W dosing, which indicates that this is a preferred dosing regimen.

[0097] FIG. 43 outlines a Phase 3 Clinical Trial assessing the dosing regimen of a 100 mg loading dose and 50 mg Q2W dosing.

DETAILED DESCRIPTION

[0098] Provided herein are novel pharmaceutical compositions comprising an antibody, in particular a monoclonal antibody, capable of binding to IGF-1R, as well as methods of making and using such pharmaceutical compositions. From one aspect, provided herein is a novel

pharmaceutical composition comprising lonigutamab, or an antigen binding fragment thereof, capable of binding to IGF-1R and, by inducing internalization of IGF-1R, being internalized into the cell. Also provided herein are certain anti-IGF-1R lonigutamab antibodies comprising a positively charged amino acid at its c-terminus (e.g., a c-terminal arginine, histidine, or lysine). Also provided herein is the use of said pharmaceutical composition comprising lonigutamab to prevent, reduce risk of developing, or treat a disease associated with IGF-1R, such as thyroid eye disease.

[0099] Certain aspects of the present disclosure are directed to pharmaceutical compositions comprising lonigutamab and methods of preventing, reducing risk of developing, or treating thyroid eye disease. Thyroid eye disease is a condition in which the eye muscles, eyelids, tear glands and fatty tissues behind the eye become inflamed. This can cause the eyes and eyelids to become red, swollen and uncomfortable and the eyes can be pushed forward ('staring' or 'bulging' eyes). In some cases there is swelling and stiffness of the muscles that move the eyes so that they no longer move in line with each other; this can cause double vision. Rarely TED can cause reduced vision from pressure on the nerve at the back of the eye or ulcers forming on the front of the eyes if the eyelids cannot close completely.

[0100] TED – also known as Graves' Orbitopathy or Ophthalmopathy – is an autoimmune condition. It occurs when the body's immune system attacks the tissue surrounding the eye causing inflammation in the tissues around and behind the eye. In most patients, the same autoimmune condition that causes TED also affects the thyroid gland, resulting in Graves' disease. Graves' disease most commonly causes thyroid overactivity (hyperthyroidism) but can also rarely cause thyroid underactivity (hypothyroidism). TED can occur in people when their thyroid is overactive, underactive or functioning normally. It can also occur after treatment for Graves' disease. People with TED need to be looked after by an eye specialist (ophthalmologist) and a thyroid specialist (endocrinologist).

[0101] The currently available therapies for treatment of TED have side-effects, including hearing impairment. These side-effects, which are reported in a substantial proportion of patients receiving currently available therapy, has limited viable therapies of treatment of patients with TED. Thus, there is an unmet need for development of therapies for treatment of TED with greater depth and durability of response, as well as improved safety profile.

Definitions

[0102] As used herein the specification, "*a*" or "*an*" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one. For example, reference to an "antibody" is a reference from one to many antibodies. As used herein "another" may mean at least a second or more.

[0103] The term "*immunoglobulin*" (Ig) is used interchangeably with "*antibody*" herein. The term "antibody" herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.,* bispecific antibodies) formed from at least two intact antibodies, antibody fragments so long as they exhibit biological activity, and antibody derivatives. The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, *see, e.g., Basic and Clinical Immunology*, 8th Ed., Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6. The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa ("κ") and lambda ("λ"), based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha ("α"), delta ("δ"), epsilon ("ε"), gamma ("γ") and mu ("μ"), respectively. The γ and α classes are further divided into subclasses (isotypes) on the basis of relatively minor differences in the CH sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known and described generally in, for example, Abbas *et al.*, Cellular and Molecular Immunology, 4th ed. (W.B. Saunders Co., 2000).

[0104] The "*variable region*" or "*variable domain*" of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the heavy chain and light chain may be referred to as "V_H" and "V_L", respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites. The variable domain mediates antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed

across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen binding site of antibodies (*see* Kabat et al., *Sequences of Immunological Interest*, Fifth Edition, National Institute of Health, Bethesda, MD (1991)). The constant domains are not involved directly in the binding of antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent-cellular toxicity.

[0105] As used herein, the term "CDR" or "complementarity determining region" is intended to mean the non-contiguous antigen binding sites found within the variable region of both heavy and light chain polypeptides. CDRs have been described by Kabat et al., J. Biol. Chem. 252:6609-6616 (1977); Kabat et al., U.S. Dept. of Health and Human Services, "Sequences of proteins of immunological interest" (1991) (also referred to herein as Kabat 1991); by Chothia et al., J. Mol. Biol. 196:901-917 (1987) (also referred to herein as Chothia 1987); and MacCallum et al., J. Mol. Biol. 262:732-745 (1996), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or grafted antibodies or variants thereof is intended to be within the scope of the term as defined and used herein. As used herein, the terms "CDR-L1", "CDR-L2", and "CDR-L3" refer, respectively, to the first, second, and third CDRs in a light chain variable region. As used herein, the terms "CDR-H1", "CDR-H2", and "CDR-H3" refer, respectively, to the first, second, and third CDRs in a heavy chain variable region. As used herein, the terms "CDR-1", "CDR-2", and "CDR-3" refer, respectively, to the first, second and third CDRs of either chain's variable region.

[0106] A number of HVR and CDR delineations are in use and are encompassed herein. The HVRs that are Kabat complementarity-determining regions (CDRs) are based on sequence variability and are the most commonly used (Kabat et al., *supra*). Chothia refers instead to the location of the structural loops (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). The AbM HVRs represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford

Molecular's AbM antibody-modeling software. The "contact" HVRs are based on an analysis of the available complex crystal structures. The residues from each of these HVRs are noted below.

Loop	Kabat	AbM	Chothia	Contact
L1	L24-L34	L24-L34	L26-L32	L30-L36
L2	L50-L56	L50-L56	L50-L52	L46-L55
L3	L89-L97	L89-L97	L91-L96	L89-L96
H1	H31-H35B	H26-H35B	H26-H32	H30-H35B (Kabat numbering)
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia numbering)
H2	H50-H65	H50-H58	H53-H55	H47-H58
H3	H95-H102	H95-H102	H96-H101	H93-H101

[0107] HVRs may comprise "extended HVRs" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2), and 89-97 or 89-96 (L3) in the VL, and 26-35 (H1), 50-65 or 49-65 (a preferred embodiment) (H2), and 93-102, 94-102, or 95-102 (H3) in the VH. The variable-domain residues are numbered according to Kabat et al., *supra*, for each of these extended-HVR definitions. The Kabat numbering system is generally used when referring to a residue in the variable domain (approximately residues 1-107 of the light chain and residues 1-113 of the heavy chain) (*e.g.*, Kabat et al., Sequences of Immunological Interest. 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The "EU numbering system" or "EU index" is generally used when referring to a residue in an immunoglobulin heavy chain constant region (*e.g.*, the EU index reported in Kabat *et al., supra*). The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody. Unless stated otherwise herein, references to residue numbers in the variable domain of antibodies means residue numbering by the Kabat numbering system. Unless stated otherwise herein, references to residue numbers in the constant domain of antibodies means residue numbering by the EU numbering system (*e.g., see* United States Patent Publication No. 2010-280227).

[0108] As used in the present specification, the expression "IGF-1R antibody" should be interpreted as similar to "anti-IGF-1R antibody" and means an antibody capable of binding to IGF-1R. In an embodiment of the present application, the epitope of the antibody is localized into the extracellular domain of the human IGF-1R (also referred as IGF-1R ECD). In a particular

embodiment, the antibody, or any antigen binding fragment thereof, is capable of binding to IGF-1R with an EC_{50} comprised between 10×10^{-10} to 1×10^{-10}, and more preferentially between 8×10^{-10} to 2×10^{-10}M. In preferred aspects of the disclosure, the anti-IGF-1R antibody is lonigutamab or a fragment, epitope, and/or derivative thereof.

[0109] The term "*monoclonal antibody*" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies of the population are identical except for possible naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen.

[0110] An "*antibody fragment*" or "*antigen-binding fragment*" or "*functional fragments*" of antibodies comprises a portion of an intact antibody, preferably the antigen binding and/or the variable region of the intact antibody or the F region of an antibody which retains or has modified FcR binding capability. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments; diabodies; and linear antibodies (*see* U.S. Patent 5,641,870, Example 2; Zapata et al., *Protein Eng.* 8(10):1057-1062 (1995)). Additional examples of antibody fragments include antibody derivatives such as single-chain antibody molecules, monovalent antibodies and multispecific antibodies formed from antibody fragments.

[0111] The term "*Fc region*" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447

residue. Suitable native-sequence Fc regions for use in the antibodies of the disclosure include human IgG1, IgG2, IgG3 and IgG4.

[0112] A "*native sequence Fc region*" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0113] A "*variant Fc region*" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, *e.g.,* from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0114] As used herein, a "chimeric antibody" refers to an antibody (immunoglobulin) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., *Proc. Nat'l Acad. Sci. USA*, 81:6851-55 (1984)). Chimeric antibodies of interest herein include PRIMATIZED® antibodies wherein the antigen-binding region of the antibody is derived from an antibody produced by, *e.g.*, immunizing macaque monkeys with an antigen of interest. As used herein, "humanized antibody" is a subset of "chimeric antibodies."

[0115] "*Humanized*" forms of non-human (*e.g.*, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. In some embodiments, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from an HVR of the recipient are replaced by residues from an HVR of a non-human species (donor

antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications may be made to further refine antibody performance, such as binding affinity. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions may include one or more individual FR residue substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, and the like. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see, e.g.*, Jones et al., *Nature* 321:522-525 (1986); Riechmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). *See also*, for example, Vaswani and Hamilton, *Ann. Allergy, Asthma & Immunol.* 1:105-115 (1998); Harris, *Biochem. Soc. Transactions* 23:1035-1038 (1995); Hurle and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Patent Nos. 6,982,321 and 7,087,409.

[0116] A "*human antibody*" is one that possesses an amino-acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., *J. Immunol.*, 147(1):86-95 (1991). *See also* van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5:368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e.g.*, immunized xenomice (*see, e.g.*, U.S. Patent Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). *See also*, for

example, Li et al., *Proc. Nat'l Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[0117] An "*acceptor human framework*" as used herein is a framework comprising the amino acid sequence of a VL or VH framework derived from a human immunoglobulin framework or a human consensus framework. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain pre-existing amino acid sequence changes. In some embodiments, the number of pre-existing amino acid changes are 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, or 2 or fewer. Where pre-existing amino acid changes are present in a VH, preferable those changes occur at only three, two, or one of positions 71H, 73H and 78H; for instance, the amino acid residues at those positions may by 71A, 73T and/or 78A. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0118] A "*human consensus framework*" is a framework that represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991). Examples include for the VL, the subgroup may be subgroup kappa I, kappa II, kappa III or kappa IV as in Kabat *et al., supra.* Additionally, for the VH, the subgroup may be subgroup I, subgroup II, or subgroup III as in Kabat *et al., supra.*

[0119] An "*amino-acid modification*" at a specified position refers to the substitution or deletion of the specified residue, or the insertion of at least one amino acid residue adjacent the specified residue. Insertion "adjacent" to a specified residue means insertion within one to two residues thereof. The insertion may be N-terminal or C-terminal to the specified residue. The preferred amino acid modification herein is a substitution.

[0120] "*Identity*", as used herein, indicates that at any particular position in the aligned sequences, the amino acid residue is identical between the sequences. "Similarity", as used herein, indicates that, at any particular position in the aligned sequences, the amino acid residue is of a similar type between the sequences. For example, leucine may be substituted for isoleucine or valine. Other amino acids which can often be substituted for one another include but are not limited to:

- phenylalanine, tyrosine and tryptophan (amino acids having aromatic side chains);
- lysine, arginine and histidine (amino acids having basic side chains);
- aspartate and glutamate (amino acids having acidic side chains);
- asparagine and glutamine (amino acids having amide side chains); and
- cysteine and methionine (amino acids having sulphur-containing side chains).

[0121] Degrees of identity and similarity can be readily calculated. (*See e.g.,* Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing. Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991)

[0122] As used herein, an "*interaction*" between IGF-1R and a second protein encompasses, without limitation, protein-protein interaction, a physical interaction, a chemical interaction, binding, covalent binding, and ionic binding. As used herein, an antibody "inhibits interaction" between two proteins when the antibody disrupts, reduces, or completely eliminates an interaction between the two proteins. An antibody of the present disclosure, or fragment thereof, "inhibits interaction" between two proteins when the antibody or fragment thereof binds to one of the two proteins.

[0123] As used herein, "*percent (%) amino acid sequence identity*" and "*homology*" with respect to a peptide, polypeptide or antibody sequence refers to the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms known in the art needed to achieve maximal

alignment over the full length of the sequences being compared. The term "*preventing*" is art-recognized, and when used in relation to a condition, such as thyroid eye disease (TED) related symptoms, relative to a patient who does not receive the therapy.

[0124] "*Restoring*" refers to the act of returning to a normal or healthy condition. The restoration may be partial (e.g., when the subject returns to a condition which is below the normal or healthy condition) or total (e.g., when the subject returns to a condition which is identical or almost identical to a normal or healthy condition). An example of a normal or healthy condition is the visual acuity of a patient prior to Thyroid Eye Disease (TED).

[0125] As use herein, the term "*specifically recognizes*" or "*specifically binds*" refers to measurable and reproducible interactions such as attraction or binding between a target and an antibody that is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody that specifically or preferentially binds to a target or an epitope is an antibody that binds this target or epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets or other epitopes of the target. It is also understood that, for example, an antibody (or a moiety) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "*specific binding*" or "*preferential binding*" does not necessarily require (although it can include) exclusive binding. An antibody that specifically binds to a target may have an association constant of at least about 10^3 M^{-1} or 10^4 M^{-1}, sometimes about 10^5 M^{-1} or 10^6 M^{-1}, in other instances about 10^6 M^{-1} or 10^7 M^{-1}, about 10^8 M^{-1} to 10^9 M^{-1}, or about 10^{10} M^{-1} to 10^{11} M^{-1} or higher. A variety of immunoassay formats can be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with a protein. *See, e.g.*, Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Publications, New York, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity.

[0126] The term "*subject*" as used herein refers to a living mammal and may be interchangeably used with the term "patient". Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such

as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. The term does not denote a particular age or gender.

[0127] The term "*therapeutically effective amount*" of a compound with respect to the subject method of treatment refers to an amount of the compound(s) in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, *e.g.,* at a reasonable benefit/risk ratio applicable to any medical treatment. A therapeutically effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual.

[0128] As used herein, the term "*treating*" or "*treatment*" includes reducing, arresting, or reversing the symptoms, clinical signs, or underlying pathology of a condition to stabilize or improve a subject's condition or to reduce the likelihood that the subject's condition will worsen as much as if the subject did not receive the treatment. "*Improving vision*" refers to the act of enhancing the faculty or state of being able to see, relative to before treatment, including improving acuity, sensitivity, and/or range of visual field.

Antibodies

[0129] In certain aspects, provided herein are pharmaceutical compositions comprising the anti-IGF-1R antibody lonigutamab.

[0130] The insulin-like growth factor 1 receptor called IGF-1R (also called IGF1R or IGF-IR) is a receptor with tyrosine kinase activity having 70% homology with the insulin receptor IR. IGF-1R is a glycoprotein of molecular weight approximately 320 kDa. It is a hetero-tetrameric receptor of which each half-linked by disulfide bridges—is composed of an extracellular α-subunit and of a transmembrane β-subunit. IGF-1R binds IGF1 and IGF2 with a very high affinity (Kd #1 nM) but is equally capable of binding to insulin with an affinity 100 to 1000 times lower. Conversely, the IR binds insulin with a very high affinity although the IGFs only bind to the insulin receptor with a 100 times lower affinity.

[0131] The tyrosine kinase domains of IGF-1R and of IR have a very high sequence homology although the zones of weaker homology respectively concern the cysteine-rich region situated on the α-subunit and the C-terminal part of the β-subunit. The sequence differences observed in the

α-subunit are situated in the binding zone of the ligands and are therefore at the origin of the relative affinities of IGF-1R and of IR for the IGFs and insulin respectively. The differences in the C-terminal part of the β-subunit result in a divergence in the signaling pathways of the two receptors; IGF-1R mediating mitogenic, differentiation and anti-apoptosis effects, while the activation of the IR principally involves effects at the level of the metabolic pathways. The cytoplasmic tyrosine kinase proteins are activated by the binding of the ligand to the extracellular domain of the receptor.

[0132] The activation of the kinases in its turn involves the stimulation of different intra-cellular substrates, including IRS-1, IRS-2, Shc and Grb 10. The two major substrates of IGF-1R are IRS and Shc which mediate, by the activation of numerous effectors downstream, the majority of the growth and differentiation effects connected with the attachment of the IGFs to this receptor. The availability of substrates can consequently dictate the final biological effect connected with the activation of the IGF-1R. When IRS-1 predominates, the cells tend to proliferate and to transform. When Shc dominates, the cells tend to differentiate. It seems that the route principally involved for the effects of protection against apoptosis is the phosphatidyl-inositol 3-kinases (PI 3-kinases) route.

[0133] In certain embodiments, antibodies, such as lonigutamab, present a high ability to be internalized following IGF-1R binding. As used herein, an antibody that "is internalized" or that "internalized" is one that is taken up by (meaning it "enters") the cell upon binding to IGF-1R on a mammalian cell. Certain anti-IGF-1R antibodies provided herein are disclosed in U.S. Pat. No. 10,202,458, which is hereby incorporated by reference for the antibodies, antibody sequences, and related compositions that it discloses.

[0134] In certain embodiments, the anti-IGF-1R antibody is lonigutamab or an anti-IGF-1R antibody derived from lonigutamab (e.g., sharing at least one CDR, such as CDRH3, with lonigutamab).

[0135] "Lonigutamab" means herein the humanized monoclonal antibody against IGF-1R that comprises a CDRH1 of SEQ ID NO: 1, a CDRH2 of SEQ ID NO: 2, a CDRH3 of SEQ ID NO: 3, a CDRL1 of SEQ ID NO: 4, a CDRL2 of SEQ ID NO: 5, and a CDRL3 of SEQ ID NO: 6, as set forth in the table below. As exemplified herein, lonigutamab comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 7 and light chain variable domain

comprising an amino acid sequence of SEQ ID NO: 8. As exemplified herein, lonigutamab comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and light chain comprising an amino acid sequence of SEQ ID NO: 10.

CDR	SEQUENCE	SEQ ID NO
CDRH1	GYTFTSYY	1
CDRH2	IWPGDGST	2
CDRH3	ASPMITPNYAMDY	3
CDRL1	QDISKY	4
CDRL2	YTS	5
CDRL3	QQGSTLPYT	6

[0136] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain variable region comprising an amino acid sequence of: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDGST**KYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQGTLVTVSS (SEQ ID NO: 7). In some embodiments, the heavy chain variable region comprises as sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 7. In certain embodiments, the heavy chain variable region comprises a sequence that is identical to SEQ ID NO: 7, but for no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions, additions and/or deletions. In certain embodiments, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the amino acid substitutions, additions and/or deletions occur outside of the heavy chain CDR domains.

[0137] In some embodiments, the anti-IGF-1R antibody comprises a light chain variable region comprising an amino acid sequence of: DIQMTQSPSSLSASVGDRVTITCRAS**QDISKY**LNWYQQKPGKAPKLLIY**YTS**RLQSGVPSRFSGRGSGTDYSLTISSLQPEDFATYFC**QQGSTLPYT**FGGGTKVEIK (SEQ ID NO: 8).

[0138] In some embodiments, the light chain variable region comprises as sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 8. In certain embodiments, the light chain variable region comprises a sequence that is identical to

SEQ ID NO: 8, but for no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions, additions and/or deletions. In certain embodiments, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the amino acid substitutions, additions and/or deletions occur outside of the light chain CDR domains.

[0139] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:9). In some embodiments, the heavy chain comprises as sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 9. In certain embodiments, the heavy chain comprises a sequence that is identical to SEQ ID NO: 9, but for no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions, additions and/or deletions. In certain embodiments, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the amino acid substitutions, additions and/or deletions occur outside of the heavy chain CDR domains.

[0140] In some embodiments, the antibody comprises a heavy chain further comprising a charged amino acid at its c-terminus (e.g., a c-terminal arginine, histidine, lysine, aspartic acid, or glutamic acid). In some embodiments, the charged amino acid is a positively charged amino acid (e.g., arginine, histidine, or lysine). In some embodiments the charged amino acid is a negatively charged amino acid (e.g., aspartic acid, or glutamic acid).

[0141] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of: QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF

PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:11).

[0142] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGH (SEQ ID NO:12).

[0143] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGR (SEQ ID NO:13).

[0144] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP

APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGD (SEQ ID NO:14).

[0145] In some embodiments, the anti-IGF-1R antibody comprises a heavy chain comprising an amino acid sequence of:
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYY**IHWVRQAPGQGLEWMGW**IWPGDG**
STKYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYFC**ASPMITPNYAMDY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGE (SEQ ID NO:15).

[0146] In some embodiments, the anti-IGF-1R antibody comprises a light chain comprising an amino acid sequence of:
DIQMTQSPSSLSASVGDRVTITCRAS**QDISKY**LNWYQQKPGKAPKLLIY**YTS**RLQSGVPS
RFSGRGSGTDYSLTISSLQPEDFATYFC**QQGSTLPYT**FGGGTKVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 10). In some embodiments, the light chain comprises as sequence that is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 10. In certain embodiments, the light chain comprises a sequence that is identical to SEQ ID NO: 10, but for no more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions, additions and/or deletions. In certain embodiments, the amino acid substitutions are conservative amino acid substitutions. In some embodiments, the amino acid substitutions, additions and/or deletions occur outside of the heavy chain CDR domains.

[0147] Full-length antibodies may be prepared by the use of recombinant DNA engineering techniques. Such engineered versions include those created, for example, from natural antibody variable regions by insertions, deletions or changes in or to the amino acid sequences of the natural antibodies. Particular examples of this type include those engineered variable region domains

containing at least one CDR and optionally one or more framework amino acids from one antibody and the remainder of the variable region domain from a second antibody. The DNA encoding the antibody may be prepared by deleting all but the desired portion of the DNA that encodes the full-length antibody. DNA encoding chimerized antibodies may be prepared by recombining DNA substantially or exclusively encoding human constant regions and DNA encoding variable regions derived substantially or exclusively from the sequence of the variable region of a mammal other than a human. DNA encoding humanized antibodies may be prepared by recombining DNA encoding constant regions and variable regions other than the complementarity determining regions (CDRs) derived substantially or exclusively from the corresponding human antibody regions and DNA encoding CDRs derived substantially or exclusively from a mammal other than a human.

[0148] Suitable sources of DNA molecules that encode antibodies include cells, such as hybridomas, that express the full-length antibody. For example, the antibody may be isolated from a host cell that expresses an expression vector that encodes the heavy and/or light chain of the antibody.

[0149] Antibody fragments, including but not limited to Fab fragments, and/or antibody derivatives may also be prepared by the use of recombinant DNA engineering techniques involving the manipulation and re-expression of DNA encoding antibody variable and constant regions. Standard molecular biology techniques may be used to modify, add or delete further amino acids or domains as desired. Any alterations to the variable or constant regions are still encompassed by the terms 'variable' and 'constant' regions as used herein. In some instances, PCR is used to generate an antibody fragment by introducing a stop codon immediately following the codon encoding the interchain cysteine of C_H1, such that translation of the C_H1 domain stops at the interchain cysteine. Methods for designing suitable PCR primers are well known in the art and the sequences of antibody C_H1 domains are readily available. In some embodiments, stop codons may be introduced using site-directed mutagenesis techniques.

[0150] An antibody of the present disclosure may be derived from any antibody isotype ("class") including for example IgG, IgM, IgA, IgD and IgE and subclasses thereof, including for example IgG1, IgG2, IgG3 and IgG4. In certain preferred embodiments, the heavy and light chains of the antibody are from IgG. The heavy and/or light chains of the antibody may be from murine IgG or human IgG. In certain other preferred embodiments, the heavy and/or light chains of the antibody

are from human IgG1. In still other preferred embodiments, the heavy and/or light chains of the antibody are from human IgG4.

[0151] An antibody of the present disclosure may be a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a humanized antibody, a human antibody, a chimeric antibody, a multispecific antibody, an antibody fragment thereof, or a derivative thereof. In some embodiments, the antibody is humanized antibody.

[0152] The antibodies of the present disclosure may also be an antibody fragment, such as a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In some embodiments, the antibody fragment is a Fab fragment.

[0153] In some embodiments, antibodies are human monoclonal antibodies which may be prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline and/or non-germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0154] In some embodiments, antibodies are humanized and/or chimeric monoclonal antibodies, which can be raised by immunizing rodents (*e.g.,* mice, rats, hamsters and guinea pigs) with either (1) the native IGF-1R derived from enzymatic digestion of a purified IGF-1R from human plasma or serum, or (2) a recombinant IGF-1R, or its derived fragment, expressed by either eukaryotic or prokaryotic systems. Other animals can be used for immunization, *e.g.,* non-human primates, transgenic mice expressing human immunoglobulins, and severe combined immunodeficient (SCID) mice transplanted with human B-lymphocytes.

[0155] Polyclonal and monoclonal antibodies are naturally generated as immunoglobulin (Ig) molecules in the immune system's response to a pathogen. A dominating format with a concentration of 8 mg/ml in human serum, the ~150-kDa IgG1 molecule is composed of two identical ~50-kDa heavy chains and two identical ~25-kDa light chains.

[0156] Hybridomas can be generated by conventional procedures by fusing B-lymphocytes from the immunized animals with myeloma cells. In addition, antibodies can be generated by screening recombinant single-chain Fv or Fab libraries from human B-lymphocytes in a phage-display system. The specificity of the MAbs to human IGF-1R can be tested by enzyme linked immunosorbent assay (ELISA), Western immunoblotting, or other immunochemical techniques.

Nucleic acids, vectors and host cells

[0157] Antibodies suitable for use in the methods of the present disclosure may be produced using recombinant methods and compositions, *e.g.,* as described in U.S. Patent No. 4,816,567. In some embodiments, isolated nucleic acids having a nucleotide sequence encoding any of the antibodies of the present disclosure are provided. Such nucleic acids may encode an amino acid sequence containing the V_L/C_L and/or an amino acid sequence containing the V_H/C_H1 of the anti-IGF-1R antibody. In some embodiments, one or more vectors (*e.g.,* expression vectors) containing such nucleic acids are provided. A host cell containing such nucleic acid may also be provided. The host cell may contain (*e.g.,* has been transduced with): (1) a vector containing a nucleic acid that encodes an amino acid sequence containing the V_L/C_L of the antibody and an amino acid sequence containing the V_H/C_H1 of the antibody, or (2) a first vector containing a nucleic acid that encodes an amino acid sequence containing the V_L/C_L of the antibody and a second vector containing a nucleic acid that encodes an amino acid sequence containing the V_H/C_H1 of the antibody. In some embodiments, the host cell is eukaryotic, *e.g.,* a Chinese Hamster Ovary (CHO) cell or lymphoid cell *(e.g.,* Y0, NS0, Sp20 cell). In some embodiments, the host cell is a bacterium such as E. coli.

[0158] Methods of making an anti-IGF-1R antibody are disclosed herein. The method includes culturing a host cell of the present disclosure containing a nucleic acid encoding the anti-IGF-1R antibody, under conditions suitable for expression of the antibody. In some embodiments, the antibody is subsequently recovered from the host cell (or host cell culture medium).

[0159] For recombinant production of a humanized anti-IGF-1R antibody of the present disclosure, a nucleic acid encoding the antibody is isolated and inserted into one or more vectors

for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.,* by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0160] Suitable vectors containing a nucleic acid sequence encoding any of the antibodies of the present disclosure, or fragments thereof polypeptides (including antibodies) described herein include, without limitation, cloning vectors and expression vectors. Suitable cloning vectors can be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, *e.g.,* pUC18, pUC19, Bluescript (*e.g.,* pBS SK+) and its derivatives, mpl8, mpl9, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Stratagene, and Invitrogen.

[0161] The vectors containing the nucleic acids of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (*e.g.,* where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell. In some embodiments, the vector contains a nucleic acid containing one or more amino acid sequences encoding an anti-IGF-1R antibody of the present disclosure.

[0162] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells. For example, an anti-IGF-1R antibody of the present disclosure may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria (*e.g.,* U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523; and Charlton, *Methods in Molecular Biology, Vol.* 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli.*). In other embodiments, the antibody of the present disclosure may be produced in eukaryotic cells, *e.g.,* a Chinese Hamster Ovary (CHO) cell or lymphoid cell *(e.g.,*

Y0, NS0, Sp20 cell) (*e.g.*, U.S. Pat. App. No. 14/269,950, U.S. Pat. No. 8,981,071, *Eur J Biochem.* 1991 Jan 1;195(1):235-42). After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

Pharmaceutical Compositions and Administration

[0163] The present disclosure is generally directed to pharmaceutical compositions comprising anti-IGF-1R antibodies disclosed herein, in particular lonigutamab. As used herein, the expression "pharmaceutical composition (also referred to as a "pharmaceutical formulation") means a combination of at least one active ingredient (e.g., lonigutamab), and at least one inactive ingredient which, when combined with the active ingredient and/or one or more additional inactive ingredients, is suitable for therapeutic administration to a human or non-human animal.

[0164] In certain aspects, provided herein is a pharmaceutical composition comprising: (a) at least 10 mg/ml of lonigutamab; (b) from 20 to 30 mM histidine; and (c) from 4% to 6% D-sorbitol; wherein the pharmaceutical composition is at a pH of from 5.5-6.5.

[0165] In certain embodiments, the pharmaceutical composition comprises at least 10 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 20 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 25 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 30 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 40 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 50 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 60 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 70 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 75 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 80 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 90 mg/ml lonigutamab. In certain embodiments, the pharmaceutical composition comprises at least 100 mg/ml lonigutamab. In some embodiments, the pharmaceutical composition comprises at least 110 mg/ml, at least 125 mg/ml, at least 150 mg/ml, at least 175 mg/ml, at least 200 mg/ml, or at least 250 mg/ml of lonigutamab. In certain embodiments, the pharmaceutical composition comprises from 75 mg/ml to 300 mg/ml, from 100 mg/ml to 300 mg/ml, or from 125 mg/ml to 250 mg/ml of

lonigutamab. In some embodiments, the pharmaceutical composition comprises about 125 mg/ml, about 150 mg/ml, about 175 mg/ml, about 200 mg/ml, or about 250 mg/ml of lonigutamab.

[0166] In some embodiments, the pharmaceutical composition comprising lonigutamab comprises from 20 to 30 mM histidine. In certain embodiments, the pharmaceutical composition comprises about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, about 25 mM, about 26 mM, about 27 mM, about 28 mM, about 29 mM, or about 30 mM histidine.

[0167] In some embodiments, the pharmaceutical composition comprising lonigutamab comprises from 4% to 6% D-sorbitol. In certain embodiments, the pharmaceutical composition comprises about 4%, 5%, or 6% D-sorbitol.

[0168] In some embodiments, the pharmaceutical composition comprising lonigutamab is at a pH of from 5.5-6.5. In certain embodiments, the pharmaceutical composition is at a pH of about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, or about 6.5.

[0169] In some embodiments, the pharmaceutical composition comprising lonigutamab does not comprise polysorbate 80. In some embodiments, the pharmaceutical composition comprises a small amount of polysorbate 80 (e.g., less than 0.05%). In certain embodiments, the pharmaceutical composition comprises no more than 0.05% polysorbate 80. In some embodiments, the pharmaceutical composition comprises no more than 0.02% polysorbate 80. In some embodiments, the pharmaceutical composition comprises no more than 0.01% polysorbate 80. In some embodiments, the pharmaceutical composition comprises no more than 0.005% polysorbate 80. In certain embodiments, the pharmaceutical composition further comprises from 0.002% to 0.05% polysorbate 80. In some embodiments, the pharmaceutical composition comprises about 0.002%, about 0.003%, about 0.004%, about 0.005%, about 0.006%, about 0.007%, about 0.008%, about 0.009%, about 0.01%, about 0.015%, about 0.02%, about 0.025%, about 0.03%, about 0.035%, about 0.04%, about 0.045%, or about 0.05% polysorbate 80.

[0170] In some embodiments, the pharmaceutical composition comprising lonigutamab does not comprise poloxamer 188. In some embodiments, the pharmaceutical composition comprises a small amount of poloxamer 188 (e.g., less than 0.1%) as a surfactant. In certain embodiments, the pharmaceutical composition comprises no more than 0.1% poloxamer 188. In some embodiments, the pharmaceutical composition comprises no more than 0.05% poloxamer 188. In some embodiments, the pharmaceutical composition comprises no more than 0.02% poloxamer 188. In

some embodiments, the pharmaceutical composition comprises no more than 0.01% poloxamer 188. In some embodiments, the pharmaceutical composition further comprises from 0.01% to 0.1% poloxamer 188. In certain embodiments, the pharmaceutical composition comprises about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, or about 0.1% poloxamer 188.

[0171] In a preferred embodiment, the pharmaceutical composition comprises: (i) about 20-200 mg/ml lonigutamab; (ii) about 10-50 mM L-histidine; (iii) between 0% (w/v) and about 10% (w/v) sorbitol; and (iv) between 0% and about 0.1% polysorbate 80. In a preferred embodiment, the pharmaceutical composition comprises about 40-100 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises about 50 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises about 100 mg/ml lonigutamab. In a preferred embodiment, the pharmaceutical composition comprises: (i) about 50 mg/ml lonigutamab; (ii) about 25 mM L-histidine; (iii) about 5% (w/v) sorbitol; and (iv) about 0.02% polysorbate 80 at pH 6.0. In a preferred embodiment, the pharmaceutical composition comprises: (i) about 100 mg/ml lonigutamab; (ii) about 25 mM L-histidine; (iii) about 5% (w/v) sorbitol; and (iv) about 0.02% polysorbate 80 at pH 6.0.

[0172] In certain embodiments, the pharmaceutical compositions comprising lonigutamab provided herein exhibit high levels of stability. The term "stable," as used herein in reference to the pharmaceutical compositions, means that the antibodies within the pharmaceutical compositions retain an acceptable degree of structure and/or function and/or biological activity after storage for a defined amount of time. A composition may be stable even though the antibody contained therein does not maintain 100% of its structure and/or function and/or biological activity after storage for a defined amount of time. Under certain circumstances, maintenance of about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98% or about 99% of an antibody's structure and/or function and/or biological activity after storage for a defined amount of time may be regarded as "stable."

[0173] Stability can be measured, *inter alia*, by determining the percentage of native antibody remaining in the composition after storage for a defined amount of time at a given temperature. The percentage of native antibody can be determined by, inter alia, size exclusion chromatography (e.g., size exclusion high performance liquid chromatography [SE-HPLC]). An "acceptable degree of stability," as that phrase is used herein, means that at least 90% of the monomeric form of the

antibody can be detected in the composition after storage for a defined amount of time at a given temperature.

[0174] In certain embodiments, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of the monomeric form of the lonigutamab antibody can be detected in the composition after storage for a defined amount of time at a given temperature. The defined amount of time after which stability is measured can be 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, or more. The temperature at which the pharmaceutical composition may be stored when assessing stability can be any temperature from about −80° C. to about 45° C., e.g., storage at about −30° C., about −20° C., about 0° C., about 5° C., about 25° C., or about 45° C. For example, a pharmaceutical composition may be deemed stable if after 3 months of storage at 5° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC. A pharmaceutical composition may also be deemed stable if after 6 months of storage at 5° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC. A pharmaceutical composition may also be deemed stable if after 9 months of storage at 5° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC. A pharmaceutical composition may also be deemed stable if after 3 months of storage at 25° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC. A pharmaceutical composition may also be deemed stable if after 6 months of storage at 25° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC. A pharmaceutical composition may also be deemed stable if after 9 months of storage at 25° C., greater than about 90%, 95%, 96% or 97% of monomeric antibody is detected by SE-HPLC.

[0175] Other methods may be used to assess the stability of the pharmaceutical compositions comprising lonigutamab disclosed herein, such as, e.g., differential scanning calorimetry (DSC) to determine thermal stability, controlled agitation to determine mechanical stability, and absorbance at about 350 nm or about 405 nm to determine solution turbidities. For example, a pharmaceutical composition disclosed herein may be considered stable if, after 6 or more months of storage at about 5° C. to about 25° C., the change in OD_{405} of the composition is less than about 0.05 (e.g., 0.04, 0.03, 0.02, 0.01, or less) from the OD_{405} of the composition at t=0.

[0176] Stability may also be assessed by measuring the biological activity and/or binding affinity of the antibody to its target. For example, a composition disclosed herein may be regarded as stable if, after storage at e.g., 5° C., 25° C., 45° C., etc. for a defined amount of time (e.g., 1 to 12 months), the anti-IGF-1R antibody contained within the composition binds to IGF-1R with an affinity that is at least 50%, 60%, 70%, 80%, 90%, 95%, or more of the binding affinity of the antibody prior to said storage. Additional methods for assessing the stability of an antibody in composition are demonstrated in the Examples presented below.

[0177] In certain embodiments, after 12 weeks at -20°C and 2-8°C, the pharmaceutical compositions comprising lonigutamab provided herein continue to display very good stability in terms of low aggregation; confirmed by both visual assessment and SEC-HPLC. The data from SEC-HPLC reveals no appreciable increase in high molecular weight species (HMWS) from T0 – T12w, with both temperatures performing comparably. CEX-HPLC analysis reveals that the compositions show good chemical stability after 12 weeks at -20°C and 2-8°C. From the CEX-HPLC data, slightly higher values for % main species are observed for samples kept at 2-8°C. This indicates that the freeze-thaw cycles undergone by samples at -20°C do not affect aggregation but are detrimental to the chemical stability of the molecule. Improvement to chemical stability is gained from formulation 3a (in Example 1, seen at both 2-8°C and -20°C) which contains sorbitol as tonicity modifier with no added PS80.

[0178] DLS measurements reveal that particle size Z_D is virtually unchanged after 12 weeks at both temperatures. PDI values show a trend towards increasing values over the timepoints, but all compositions remain monodisperse after 12 weeks.

[0179] In some embodiments, the pharmaceutical composition comprising lonigutamab is stable for at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks, or at least 16 weeks. In some embodiments, the pharmaceutical composition is stable at a temperature of from -20°C to 8°C.

[0180] In the fluid form, the pharmaceutical compositions provided herein may, in certain embodiments, exhibit low to moderate levels of viscosity. "Viscosity" as used herein may be "kinematic viscosity" or "absolute viscosity." "Kinematic viscosity" is a measure of the resistive flow of a fluid under the influence of gravity. When two fluids of equal volume are placed in identical capillary viscometers and allowed to flow by gravity, a viscous fluid takes longer than a less viscous fluid to flow through the capillary. For example, if one fluid takes 200 seconds to

complete its flow and another fluid takes 400 seconds, the second fluid is twice as viscous as the first on a kinematic viscosity scale. "Absolute viscosity", sometimes called dynamic or simple viscosity, is the product of kinematic viscosity and fluid density (Absolute Viscosity=Kinematic Viscosity×Density). The dimension of kinematic viscosity is L^2/T where L is a length and T is a time. Commonly, kinematic viscosity is expressed in centistokes (cSt). The System International (SI) unit of kinematic viscosity is mm^2/s, which is 1 cSt. Absolute viscosity is expressed in units of centipoise (cP). The SI unit of absolute viscosity is the milliPascal-second (mPa·s), where 1 cP=1 mPa·s.

[0181] As used herein, a low level of viscosity, in reference to a pharmaceutical composition comprising lonigutamab disclosed herein, will exhibit an absolute viscosity of less than about 20 cPoise (cP). For example, a pharmaceutical composition disclosed herein will be deemed to have "low viscosity," if, when measured using standard viscosity measurement techniques, the composition exhibits an absolute viscosity of about 19 cP, about 18 cP, about 17 cP, about 16 cP, about 15 cP, about 14 cP, about 13 cP, about 12 cP, about 11 cP, about 10 cP, about 9 cP, about 8 cP, about 7 cP, about 6 cP, about 5 cP, about 4 cP, or less at 21°C. As used herein, a moderate level of viscosity, in reference to a pharmaceutical composition disclosed herein, will exhibit an absolute viscosity of between about 30 cP and about 20 cP at 21°C. For example, a pharmaceutical composition disclosed herein will be deemed to have "moderate viscosity," if when measured using standard viscosity measurement techniques, the composition exhibits an absolute viscosity of about 30 cP, about 29 cP, about 28 cP, about 27 cP, about 26 cP, about 25 cP, about 24 cP, about 23 cP, about 22 cP, about 21 cP or about 20 cP at 21°C.

[0182] In some embodiments, the osmolality of the pharmaceutical composition comprising lonigutamab is within physiological osmolality range of 250-400mOsm/kg. In some embodiments, the viscosity of the pharmaceutical composition is no more than 30 cP at 21°C. In some embodiments, the viscosity of the pharmaceutical composition is no more than 15 cP at 21°C. In some embodiments, the viscosity of the pharmaceutical composition is about 10 cP, about 11 cP, about 12 cP, about 13 cP, about 14 cP, about 15 cP, about 16 cP, about 17 cP, about 18 cP, about 19 cP, about 20 cP, about 21 cP, about 22 cP, about 23 cP, about 24 cP, about 25 cP, about 26 cP, about 27 cP, about 28 cP, about 29 cP, or about 30 cP at 21°C.

Injectors

[0183] In certain aspects, the present disclosure relates to an injector comprising the pharmaceutical composition comprising lonigutamab disclosed herein. In some embodiments, the injector comprises a delivery volume of no more than 2 ml. In some embodiments, the injector comprises a needle of a size of no bigger than 24G (e.g., 25G, 26G, 27G). In some embodiments, the injector comprises a needle of a size of no bigger than 25G. In some embodiments, the injector comprises a needle of a size of no bigger than 26G. In some embodiments, the injector comprises a needle of a size of no bigger than 27G. In some embodiments, the injector is an automatic reusable fix dose Pen. In some embodiments, the injector is an automatic reusable variable dose Pen. In some embodiments, the injector is an automatic disposable fix dose autoinjector.

[0184] In some embodiments, the pharmaceutical compositions comprising lonigutamab provided herein may be contained within any container suitable for storage of medicines and other therapeutic compositions. For example, the pharmaceutical compositions may be contained within a sealed and sterilized plastic or glass container having a defined volume such as a vial, ampule, syringe, cartridge, or bottle. Different types of vials can be used to contain the compositions provided herein, including, e.g., clear and opaque (e.g., amber) glass or plastic vials. Likewise, any type of syringe can be used to contain and/or administer the pharmaceutical compositions disclosed herein.

[0185] The pharmaceutical compositions comprising lonigutamab provided herein may be contained within "normal tungsten" syringes or "low tungsten" syringes. As will be appreciated by persons of ordinary skill in the art, the process of making glass syringes generally involves the use of a hot tungsten rod which functions to pierce the glass thereby creating a hole from which liquids can be drawn and expelled from the syringe. This process results in the deposition of trace amounts of tungsten on the interior surface of the syringe. Subsequent washing and other processing steps can be used to reduce the amount of tungsten in the syringe. As used herein, the term "normal tungsten" means that the syringe contains greater than 500 parts per billion (ppb) of tungsten. The term "low tungsten" means that the syringe contains less than 500 ppb of tungsten. For example, a low tungsten syringe can contain less than about 490, 480, 470, 460, 450, 440, 430, 420, 410, 390, 350, 300, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 or fewer ppb of tungsten.

[0186] The pharmaceutical compositions comprising lonigutamab provided herein may be contained within plastic syringes. In the last decade, pharmaceutical protein and peptide drug

products have been approved for use with prefilled plastic syringes. For example, the pharmaceutical compositions may be contained in a Daikyo Crystal Zenith (CZ) syringe (Daikyo Seiko, Tokyo).

[0187] The rubber plungers used in syringes, and the rubber stoppers used to close the openings of vials, may be coated to prevent contamination of the medicinal contents of the syringe or vial and/or to preserve their stability. Thus, pharmaceutical compositions provided herein, according to certain embodiments, may be contained within a syringe that comprises a coated plunger, or within a vial that is sealed with a coated rubber stopper. For example, the plunger or stopper may be coated with a fluorocarbon film. Examples of coated stoppers and/or plungers suitable for use with vials and syringes containing the pharmaceutical compositions disclosed herein are mentioned in, e.g., U.S. Pat. Nos. 4,997,423; 5,908,686; 6,286,699; 6,645,635; and 7,226,554, the contents of which are incorporated by reference herein in their entireties. Particular exemplary coated rubber stoppers and plungers that can be used in the methods disclosed herein are commercially available under the tradename "FluroTec®," available from West Pharmaceutical Services, Inc. (Lionville, Pa.).

[0188] In certain embodiments, the pharmaceutical compositions comprising lonigutamab can be administered to a patient by parenteral routes such as injection (e.g., subcutaneous, intravenous, intramuscular, intraperitoneal, infraorbital, intravitreal, intraocular, subconjunctival, retrobulbar, peribulbar, and/or intrathecal injection). Numerous reusable pen and/or autoinjector delivery devices can be used to subcutaneously deliver the pharmaceutical compositions disclosed herein. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen and/or autoinjector delivery devices having applications in subcutaneous delivery of a pharmaceutical composition disclosed herein include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen,

Thousand Oaks, Calif.), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L. P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park, Ill.), to name only a few.

[0189] The use of West SelfDose and SmartDose injection systems to deliver the pharmaceutical compositions disclosed herein is also contemplated herein. The use of a microinfusor to deliver the pharmaceutical compositions disclosed herein is also contemplated herein. As used herein, the term "microinfusor" means a subcutaneous delivery device designed to slowly administer large volumes (e.g., up to about 2.5 mL or more) of a therapeutic composition over a prolonged period of time (e.g., about 10, 15, 20, 25, 30 or more minutes). See, e.g., U.S. Pat. Nos. 6,629,949; 6,659,982; and Meehan et al., *J. Controlled Release* 46:107-116 (1996).

Methods of Treatment

[0190] In certain aspects, the present disclosure relates to methods of preventing, reducing risk of developing, or treating a disease or disorder associated with IGF-1R comprising administering the pharmaceutical composition comprising lonigutamab. The present disclosure is also generally directed to methods of preventing, reducing risk of developing, or treating IGF-1R related diseases and disorders comprising administering the pharmaceutical composition comprising lonigutamab. The present disclosure is also generally directed to methods of preventing, reducing risk of developing, or treating IGF-1R related diseases and disorders comprising administering the pharmaceutical composition comprising lonigutamab using the injector disclosed herein. In some embodiments, the disease or disorder is thyroid eye disease (TED).

[0191] In some embodiments, the disease or disorder is stroke, acromegaly, diabetic nephropathy (diabetic kidney disease), idiopathic pulmonary fibrosis, interstitial lung disease, obesity, type 2 diabetes, juvenile idiopathic arthritis (JIA), diffuse cutaneous systemic sclerosis, Sjogren's syndrome calcinosis and vasculitis, cachexia and sarcopenia, diabetic macular edema, arterial atherosclerosis, peripheral artery disease (PAD), myocardial infarction and stroke, diabetic foot and skin, rheumatoid arthritis, neurofibromatosis 1, neurofibromatosis 2, polycystic kidney disease, polycystic liver disease, polycystic ovarian syndrome, Alzheimer's disease, cognitive decline, dementia, depression and anxiety, asthma, aging, thyroid eye disease, idiopathic orbital inflammation, human type 2 lipodystrophy and associated cardiomyopathy, autosomal dominant polycystic kidney disease (ADPKD), NASH, Graves' disease, and/or Hashimoto's thyroiditis.

[0192] In preferred embodiments, the disease or disorder is thyroid eye disease (TED). Thyroid-associated ophthalmopathy (TAO), also known as thyroid eye disease (TED), Graves' ophthalmopathy or orbitopathy (GO), thyrotoxic exophthalmos, dysthyroid ophthalmopathy, and several other terms, is orbitopathy associated with thyroid dysfunction. TED is divided into two types. Active TED, which typically lasts 1-3 years, is characterized by an ongoing autoimmune/inflammatory response in the soft tissues of the orbit. Active TED is responsible for the expansion and remodeling of the ocular soft tissues. The autoimmune/inflammatory response of active TED spontaneously resolves and the condition transitions into inactive TED. Inactive TAO is the term used to describe the long-term/permanent sequelae of active TED. The cause of TED is unknown. TED is typically associated with Graves' hyperthyroidism, but can also occur as part of other autoimmune conditions that affect the thyroid gland and produce pathology in orbital and periorbital tissue, and, rarely, the pretibial skin (pretibial myxedema) or digits (thyroid acropachy). TED is an autoimmune orbitopathy in which the orbital and periocular soft tissues are primarily affected with secondary effects on the eye and vision. In TED, as a result of inflammation and expansion of orbital soft tissues, primarily eye muscles and adipose, the eyes are forced forward (bulge) out of their sockets— a phenomenon termed proptosis or exophthalmos. Although most cases of TED do not result in loss of vision, this condition can cause vision-threatening exposure keratopathy, troublesome diplopia (double vision), and compressive dysthyroid optic neuropathy. TED may precede, coincide with, or follow the systemic complications of dysthyroidism. The ocular manifestations of TED include upper eyelid retraction, lid lag, swelling, redness (erythema), conjunctivitis, and bulging eyes (exophthalmos or proptosis), chemosis, periorbital edema, and altered ocular motility with significant functional, social, and cosmetic consequences. Many of the signs and symptoms of TED, including proptosis and ocular congestion, result from expansion of the orbital adipose tissue and periocular muscles. The adipose tissue volume increases owing in part to new fat cell development (adipogenesis) within the orbital fat. The accumulation of hydrophilic glycosaminoglycans, primarily hyaluronic acid, within the orbital adipose tissue and the perimysial connective tissue between the extraocular muscle fibers, further expands the fat compartments and enlarges the extraocular muscle bodies. Hyaluronic acid is produced by fibroblasts residing within the orbital fat and extraocular muscles, and its synthesis in vitro is stimulated by several cytokines and growth factors, including IL-lbeta, interferon-

gamma, platelet-derived growth factor, thyroid stimulating hormone (TSH) and insulin-like growth factor I (IGF-I).

[0193] Antibodies that activate the insulin-like growth factor I receptor (IGF-IR) have also been detected and implicated in active TED. Without being bound to any theory, it is believed that TSHR and IGF-IR form a physical and functional complex in orbital fibroblasts, and that blocking IGF-IR appears to attenuate both IGF-1 and TSH-dependent signaling. It has been suggested that blocking IGF-IR using an antibody antagonist might reduce both TSHR- and IGF-I-dependent signaling and therefore interrupt the pathological activities of autoantibodies acting as agonists on either receptor.

[0194] IGF-IR is a widely expressed heterotetrameric protein involved in the regulation of proliferation and metabolic function of many cell types. It is a tyrosine kinase receptor comprising two subunits. IGF-IRalpha contains a ligand-binding domain while IGF-IRbeta is involved in signaling and contains tyrosine phosphorylation sites.

[0195] Thyroid Eye Disease (TED), is a debilitating autoimmune disorder that occurs in patients with Graves' Disease in which inflammation in the muscle and fat tissue behind the eyes results in proptosis, diplopia, redness, pain, and swelling, leading to photosensitivity, blurred vision, and in serious cases, blindness. The mechanistic underpinnings of TED involve a complex interaction between autoantibody-mediated stimulation of Thyroid Stimulating Hormone Receptor (TSHR) and Insulin-like growth factor 1 receptor (IGF-1R) signaling in orbital fibroblasts that cause orbital tissue inflammation and expansion. Current therapies include corticosteroids and teprotumumab, as well as surgical intervention to prevent vision loss. Lonigutamab is a high-affinity (K_D <50 pM) monoclonal antibody directed against IGF-1R that induces rapid and efficient receptor internalization. Lonigutamab is being developed as a potential treatment for TED. To support clinical development of Lonigutamab, a multi-color flow cytometric assay was developed to monitor the binding of Lonigutamab to IGF-1R on the surface of human Peripheral Blood Mononuclear Cells (PBMCs).

[0196] Lonigutamab is a humanized monoclonal antibody against IGF-1R. Lonigutamab has high affinity and specificity toward IGF-1R. Specifically, lonigutamab has picomolar affinity for IGF-1R. In certain preferred embodiments, lonigutamab has a k_D of about 30 pM to a binding epitope of IGF-1R. Once lonigutamab binds to IGF-1R, it induces receptor internalization, which results in signal blockade from IGF-1R, which may lead to the therapeutic effect of lonigutamab. The

IGF-1R internalization may occur within minutes after administration of pharmaceutical compositions comprising lonigutamab. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab may be attained in about an hour after administration of the pharmaceutical composition comprising lonigutamab.

[0197] As outlined in FIG. 8, Lonigutamab has unique and beneficial pharmacological properties, for example: (i) a high binding potency for IGF-1R, showing an affinity of approximately 30 pM; (ii) a unique binding epitope that is a peripheral IGF-1R binding site in contrast to other anti-IGF-1R antibodies that compete for the endogenous IGF-1 binding site; and (iii) rapid receptor internalization, which occurs within minutes of Lonigutamab binding.

[0198] As disclosed herein, Lonigutamab is the first subcutaneous anti-IGF-1R therapy to demonstrate proof of concept in TED. Based on clinical trials run in conjunction with the present Inventors treatment of TED using Lonigutamab has proved successful. Clinical trials have revealed that Lonigutamab is the first subcutaneous anti-IGF-1R therapy to demonstrate meaningful responses in Proptosis, Clinical Activity Score, and Diplopia. Further, responses have been rapid, generally occurring within 3 weeks after a single SC dose. Early results from the clinical trials described in the Examples provided herein have shown proof of concept achieved with placebo-controlled cohort (Cohort 1) supporting monthly dosing to optimize safety and efficacy. An open-label Cohort 2 validates POC and enables continued refinement of dose level and regimen.

[0199] As disclosed herein, Lonigutamab also presents a differentiated clinical profile, including: (i) being the first subcutaneous anti-IGF-1R therapy with POC in TED, which improves upon current treatment responses for therapies reliant on short-term, fixed IV dosing, which enables long-term treatment with prolonged benefits; (ii) potential with monthly SC to optimize both safety and efficacy; (iii) ability to minimize exposures; (iv) increasing duration of therapy to target greater depth and durability – more complete resolution of disease; (v) clinically meaningful responses achieved at low exposures may allow for optimization of response while avoiding hearing impairment; (vi) increasing duration of therapy with anti-IGF-1R has previously demonstrated the potential for improvements over time; and (vii) well tolerated and favorable safety profile consistent with previous anti-IGF-1R experience at a similar timepoint.

[0200] Lonigutamab has shown the ability to provide rapid responses, measured within 3 weeks after a single subcutaneous dose. The present disclosure reports the first proof of concept achieved with placebo-controlled Cohort 1 supporting monthly dosing to optimize safety and efficacy. This

has been buttressed by an open-label Cohort 2, which validates POC and enables continued refinement of dose level and regimen.

[0201] Along with rapid and meaningful clinical responses, SC administration of lonigutamab may optimize the benefit-to-risk assessment in treating patients with TED as SC administration may minimize blood-labyrinth barrier penetration to the inner ear by reducing C_{max} compared to IV administration. Concurrently, this allows lonigutamab composition of the disclosure, and methods using them, to employ patient-delivered, at-home administration via a pre-filled syringe or autoinjector, which offers a more convenient option that intravenous therapies.

[0202] Further, recent safety updates to SoC label for current IV anti-IGF-1R TED therapies highlight hearing impairment as a serious, potentially permanent effect. As disclosed herein, lonigutamab compositions of the disclosure improve upon and optimize the benefit-to-risk of anti-IGF-1R therapy side effects. Lonigutamab has demonstrated that it is a high potency anti-IGF-1R with unique impact on the IGF-1R Axis enabling the potential to optimize benefit-risk towards more complete resolution of disease, by: maximizing clinical benefit by enabling greater depth and durability of response with longer term treatment beyond the fixed regimen of standard of care; and minimizing safety liability by reducing C_{max} compared to IV therapy and penetration to the inner ear which may drive hearing impairment.

[0203] In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 70% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 80% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 85% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 90% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 95% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 97% IGF-1R internalization. In certain preferred embodiments, administration of pharmaceutical compositions comprising lonigutamab induce greater than about 99% IGF-1R internalization.

[0204] In certain embodiments of the compositions and methods provided herein, the pharmaceutical composition comprising lonigutamab is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition comprising lonigutamab is administered subcutaneously. In certain embodiments, the pharmaceutical composition comprising lonigutamab is formulated for intramuscular administration. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered intramuscularly. In some embodiments, the pharmaceutical composition comprising lonigutamab is formulated for infraorbital, intravitreal, intraocular, subconjunctival, retrobulbar, peribulbar, and/or intrathecal administration. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered by infraorbital, intravitreal, intraocular, subconjunctival, retrobulbar, peribulbar, and/or intrathecal injection.

[0205] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered in a delivery volume of no more than 3 ml, 2.5 ml, 2 ml, 1.5 ml, or 1 ml. In some embodiments, the pharmaceutical composition is administered in a delivery volume of no more than 2 ml.

[0206] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered via a needle of a size of no bigger than 24G, 25G, 26G, or 27G. In some embodiments, the pharmaceutical composition is administered in a 24G needle, a 25G needle, a 26G needle, or a 27G needle.

[0207] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered with an injection force of no more than 14N, 13N, 12N, 11N, 10N, 9N, 8N, 7N, or 6N. In some embodiments, the pharmaceutical composition is administered with an injection force of no more than 12N. In certain embodiments, the pharmaceutical composition is administered with an injection force of about 4N, about 5N, about 6N, about 7N, about 8N, about 9N, about 10N, about 11N, or about 12N.

[0208] In some embodiments, the method reduces the severity of the thyroid eye disease (TED). In some embodiments, the method reduces proptosis in an eye in a subject with thyroid eye disease (TED). In some embodiments, proptosis is reduced by at least 2 mm. In some embodiments, proptosis is reduced by at least 3 mm. In some embodiments, proptosis is reduced by at least 4 mm.

[0209] In some embodiments, the method reduces Clinical Activity Score (CAS) of thyroid eye disease (TED). In some embodiments, the clinical activity score (CAS) is reduced by at least 2 points. In some embodiments, the clinical activity score (CAS) is reduced to one (1). In some embodiments, the clinical activity score (CAS) of the subject is reduced to zero (0). In some embodiments, the method improves the quality of life in the subject. In some embodiments, the quality of life is measured by the Graves' Ophthalmopathy Quality of Life (GO-QoL) assessment. In some embodiments, the quality of life is measured by the Visual Functioning or Appearance subscale thereof. In some embodiments, the quality of life is measured by the European Group on Graves' orbitopathy (EUGOGO) guidelines. In some embodiments, the method reduces the severity of diplopia. In some embodiments, the diplopia is constant diplopia. In some embodiments, the diplopia is inconstant diplopia. In some embodiments, the diplopia is intermittent diplopia.

[0210] In certain aspects, the invention provides methods of administration of pharmaceutical compositions comprising lonigutamab. These pharmaceutical compositions may be administered to patients suffering from thyroid eye disease (TED). In certain embodiments, the pharmaceutical compositions of the invention may be administered intravenously. The methods of the invention provide intravenous infusion of pharmaceutical compositions comprising up to about 3.0 mg/kg lonigutamab to the patient. In certain embodiments, methods of the invention provide administration of pharmaceutical compositions comprising about 0.1, 0.3, 1.0, or 3.0 mg/kg of lonigutamab as an intravenous infusion. The invention further provides that the intravenous infusion may take place for a period of about 15 minutes to about 120 minutes. In certain preferred embodiments, the intravenous infusion takes place for a duration of about 60 minutes.

[0211] In certain aspects, the invention provides administration of pharmaceutical compositions comprising lonigutamab as a subcutaneous injection. In certain embodiments, the methods of the invention provide subcutaneous injection of up to about 250 mg lonigutamab.

[0212] In certain embodiments, the methods of the invention provide subcutaneous injection of up to about 10 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 225 mg, 230 mg, 240 mg, 245 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, or about 300 mg or more of lonigutamab. In certain embodiments, the pharmaceutical composition for subcutaneous administration comprises about 10 mg, 20 mg, 25 mg, 40 mg, 50 mg, 60 mg, 100

mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 225 mg, 230 mg, 240 mg, 245 mg, or 250 mg of lonigutamab mg of lonigutamab. The pharmaceutical compositions for subcutaneous administration may have a volume of from about 0.1 mL to about 3 mL. In preferred embodiments, the administered volume is up to about 1 mL. Beneficially, since the subcutaneous administration is conducted within tolerable volumes, the pharmaceutical compositions could be administered in an out-patient setting, or the pharmaceutical compositions of the invention could be self-administered by the patients. This results in a convenient and an efficient way for administration of the pharmaceutical composition comprising lonigutamab. In particular, the subcutaneous administration of pharmaceutical compositions is beneficial as compared to the intravenous administration due to the ease of administration of the pharmaceutical composition.

[0213] In certain embodiments of the invention, the administration of pharmaceutical composition comprising lonigutamab results in maximal IGF-1R receptor occupancy with the anti-IGF-1R antibody. This maximal occupancy of IGF-1R may be achieved any time after the administration of the pharmaceutical composition comprising lonigutamab. In certain embodiments, this is achieved after about 12 hours after administration of the pharmaceutical composition comprising lonigutamab. The pharmaceutical compositions administered may comprise about 50 mg to about 300 mg lonigutamab. In preferred embodiments, the pharmaceutical composition may comprise about 100 mg of lonigutamab. Notably, the maximal IGF-1R receptor occupancy may be maintained up to a few months after a single administration. In preferred embodiments, the IGF-1R receptor occupancy maintained for at least about 4 weeks after a single administration of a pharmaceutical composition comprising lonigutamab. The maximal receptor occupancy level may be maintained after a single subcutaneous injection or an intravenous infusion of pharmaceutical composition comprising lonigutamab.

[0214] Teprotumumab, a previously known antibody for IGF-1R occupancy was maintained a concentration of 200 μg/mL to have improved efficacy. Lonigutamab is approximately 75 times more potent as compared to teprotumumab, the equivalent serum concentration required to maintain therapeutic activity of lonigutamab is predicted to be around 3 μg/mL. In certain aspects, the serum concentration required for maximal IGF-1R receptor internalization is a concentration of approximately about 3 μg/mL of lonigutamab. Thus, the therapeutically effective serum concentration of lonigutamab is at least about 1 μg/mL. In certain preferred embodiments, the

therapeutically effective serum concentration of lonigutamab is at least about .1 μg/mL. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 1 μg/mL. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 2 μg/mL. In certain preferred embodiments, the therapeutically effective serum concentration of lonigutamab is at least about 3 μg/mL. Importantly, the pharmaceutical compositions of the invention provide a therapeutically effective serum concentration of lonigutamab to the patient.

[0215] In certain aspects of the invention, the pharmaceutical compositions comprising lonigutamab administered to the patients are safe and tolerable. Moreover, the pharmaceutical compositions of the invention have minimal adverse events.

[0216] In certain aspects, the invention provides methods of treatment of thyroid eye disease (TED) comprising subcutaneous administration of a pharmaceutical composition comprising from about 10 mg to about 500 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 20 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 50 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 100 mg lonigutamab. In certain embodiments, the pharmaceutical composition comprises about 250 mg lonigutamab.

[0217] In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered twice weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered thrice weekly. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered on alternate days, *i.e.*, once every two days. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every two (2) weeks. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every three (3) weeks. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered once every four (4) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every five (5) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every six (6) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every seven (7) weeks. In certain embodiments, the pharmaceutical composition comprising

lonigutamab is administered once every eight (8) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every nine (9) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every ten (10) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every eleven (11) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every twelve (12) weeks. In certain embodiments, the pharmaceutical composition comprising lonigutamab is administered once every 12 weeks or greater.

[0218] In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 14. In certain preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered, after a loading dose, at day 14 and day 21. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 21. In other preferred embodiments, the pharmaceutical composition comprising lonigutamab is administered at day 1 and day 28.

[0219] In other preferred embodiments, (i) a pharmaceutical composition comprising 100 mg lonigutamab is administered on day 1 followed by (ii) administration of a pharmaceutical composition comprising 50 mg lonigutamab on day 14, and optionally every two weeks thereafter for a time period of at least 22 weeks, 36 weeks or 50 weeks. In preferred embodiments, the pharmaceutical composition comprises (i) 50 mg/ml lonigutamab, (ii) 25 mM L-histidine, (iii) 5% (w/v) sorbitol, and (iv) 0.02% polysorbate 80, pH 6.0. In preferred aspects, an autoinjector is used administer a total volume of 1 ml of a formulation comprising 50 mg/ml lonigutamab, while the 100 mg loading dose uses two autoinjectors that contain the same 50 mg/ml lonigutamab pharmaceutical composition.

EXAMPLES

Example 1: Safety, tolerability, and pharmacokinetics

[0220] A Phase I trial was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics (PD) of single ascending doses (SAD) of IV or SC lonigutamab in healthy participants. The study conducted was a single-center, randomized, double-blind, placebo-

controlled, sequential single ascending dose (SAD) study. The study involved eight (8) cohorts of healthy volunteers, which were divided into two groups: four (4) cohorts receiving intravenous administration of lonigutamab and four (4) cohorts receiving subcutaneous administration of lonigutamab.

[0221] Specifically, cohorts 1-4 received intravenous administration of 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, or 3.0 mg/kg of lonigutamab or matching placebo over the course of 60 minutes. Cohorts 5-8 received fixed-does subcutaneous injections dose administered in a 2 mL or less volume at doses of 20 mg, 40 mg, 125 mg, or 250 mg of lonigutamab or matching placebo.

[0222] The participants in the study were healthy as per the study protocol. Specifically, the participants were aged between 18 and 55 years old, and had a body-mass index (BMI) in the range of 18 – 32 kg/m^2 when they were enrolled in the study.

[0223] In the course of the study, routine laboratory, audiology, pharmacokinetic, and pharmacodynamic assessments were performed at pre-determined time points in each of the cohort involved in the study. In addition, safety and tolerability of the administered drug were evaluated through the course of study through the assessment of adverse events and were monitored over 99 days.

[0224] The pharmacokinetic data was obtained using a validated electrochemiluminescent immunoassay. The receptor occupancy was evaluated using a qualified flow cytometry assay.

[0225] The study involved enrollment of sixty-three (63) participants. In these participants, forty-seven (47) received lonigutamab and sixteen (16) received placebo. In this study, four (4) participants discontinued because they were lost in follow up or other reasons. This loss of participants were not deemed not to impact the primary analyses.

[0226] The baseline characteristics and demographics of the participants are provided in Table A below.

Table A

Baseline Characteristics:	**Safety Population (n=63)**
Age (years)	35.7 (19-55)
Sex	
Male	48 (76.2)
Female	15(23.8)

Race	
American Indian or Alaska Native	1 (1.6)
Black/African American	34 (54)
White	23 (36.5)
Unknown	3 (4.8)
Multiple	2 (3.2)
Weight (kg)	78.2 (52.9-100.1)
BMI (kg/m^2)	25.67 (20.0-29.6)

[0227] The data in Table A is provided in n(%) or mean (range). There were no meaningful differences across treatment groups for any of the characteristics.

[0228] The preliminary data for safety and tolerability assessment obtained by tracking the treatment-emergent adverse events (TEAEs) is presented in Fig. 1.

[0229] The data demonstrates that no serious adverse events (SAEs) occurred. All the adverse events were mild and moderate in severity, and dose-related safety events occurred. Overall, the target-related adverse events of special interest (AESI) that were closely monitored for included allergic reactions type I/anaphylaxis, hyperglycemia, infusion-related reactions, diarrhea/inflammatory bowel disease exacerbation, hearing impairment, and muscle spasms. In the study, one (1.6%) AESI was observed in one (1) participant; gastrointestinal disorders (abdominal pain, abdominal distention, and frequent bowel movements) that were "possibly" or "probably" related to lonigutamab (participant reported more than 1 TEAE) in the 20 mg SC cohort.

[0230] One participant had an infusion-related reaction and three (3) had injection site reactions that were "possibly" or "probably" related to lonigutamab. All reactions were mild and self-limited, resolving within a few hours without medical intervention.

Pharmacokinetic assessments:

[0231] The mean serum lonigutamab concentration over time profiles following intravenous (IV) administration is presented in FIG. 2. The mean serum lonigutamab concentration over time profiles following subcutaneous (SC) administration is presented in FIG. 3.

[0232] In the data provided in Figures 17 and 18, samples below the limit of quantification (0.1 µg/mL) are plotted as 0 µg/mL in the 3.0 mg/kg, n does not include 1 participant who discontinued

early in the study due to deployment, as previously noted. The shaded area in FIG. 2 and FIG. 3 represents the serum concentrations of lonigutamab, which were above the IGF-1R internalization saturation.

[0233] As evident from the data provided in FIG. 2 and FIG. 3, mean serum concentrations of lonigutamab increased in a greater than dose proportional manner over the dose ranges tested. Moreover, FIG. 2 and FIG. 3 also provide indication of target-mediated drug disposition (TMDD) after the administration of IV and/or SC administration of lonigutamab. TMDD describes a nonlinear pharmacokinetics (PK) phenomenon that is caused by high-affinity binding of a compound to its pharmacologic targets. Once lonigutamab binds to IGF-1R, the resulting complex is degraded. At low concentrations, the serum concentration of lonigutamab declines rapidly as lonigutamab efficiently binds to IGF-1R and is degraded, and thus, there is a rapid decline in the measured serum concentrations of lonigutamab. In contrast, at high concentrations, the target, IGF-1R is saturated with lonigutamab, and the serum concentrations of lonigutamab declines slowly. This slow decline of serum concentrations of lonigutamab indicates that it is available to bind to newly generated IGF-1R. In addition to the pharmacology of lonigutamab, this data provides additional evidence of IGF-1R internalization.

[0234] This data demonstrates that TMDD threshold, above which IGF-1R internalization is saturated, appears to be around 3 μg/mL lonigutamab. As compared to IV administration, SC administration of lonigutamab overcomes TMDD to maintain pharmacologically relevant concentrations of lonigutamab.

Pharmacodynamic assessments:

[0235] The mean lonigutamab receptor occupancy on peripheral blood mononuclear cells over time following intravenous administration is provided in FIG. 4. The mean lonigutamab receptor occupancy on peripheral blood mononuclear cells over time following subcutaneous administration is provided in FIG. 5. The shaded area in FIG. 4 and FIG. 5 demonstrates the area of optimal IGF-1R internalization after the administration of the pharmaceutical composition comprising lonigutamab.

[0236] As noted in the data provided in FIGS. 4 and 5, maximal IGF-1R occupancy was observed by the first timepoint (12 hours) in all cohorts. The duration of receptor saturation increased with increasing dose of lonigutamab. The 1.0 mg/kg and 3.0 mg/kg (administered as an intravenous infusion) and 125 mg and 250 mg (administered as a subcutaneous injection) were maintained at

a maximal level of receptor occupancy for a period of at least 4 weeks. As noted previously, in the 3.0 mg/kg cohort, n does not include one (1) participant who discontinued early in the study. The shaded area in FIGS. 4 and 5 indicates receptor saturation.

Example 2 - Phase 1/2, Adaptive, Multiple Dose-Ranging Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Clinical Efficacy of Lonigutamab in Subjects with Thyroid Eye Disease

[0237] This example outlines a Phase 1/2 clinical trial assessing the use of a lonigutamab composition of the present disclosure to treat TED.

Study and Dosing Rationale

[0238] The 40 mg Q3W SC dose in Cohort 1 for a 6-week treatment period was chosen as it was anticipated to be safe and well-tolerated based on available data from the completed phase 1a single ascending dose (SAD) study in healthy subjects. PD data suggest the 40 mg dose could potentially result in clinical benefit for TED patients based on maintaining full receptor occupancy (RO) in PBMCs over the dosing interval (i.e., once every 3 weeks), while a lower dose did not maintain receptor saturation at Day 19 in the Phase 1a study.

[0239] The doses for subsequent cohorts are selected as predicted to maintain a trough concentration (C_{min}) of approximately 3 μg/mL. This target trough concentration is based on published data from teprotumumab,[9] an approved IGF-1R inhibitor for the treatment of TED, which suggested maintaining C_{min} levels of 200 μg/mL or greater for that molecule supported clinical efficacy. Given a 75× potency difference between teprotumumab[3] and lonigutamab, in favor of the latter, ~3 μg/mL is the target trough concentration for lonigutamab. No exposure-response for safety events was observed with teprotumumab.

[0240] Subjects enrolled in Cohort 2 receive an initial loading dose of 50 mg of lonigutamab followed by 11 weekly (QW) doses of 25 mg of lonigutamab.

[0241] The dose selected for Cohort 3 aims to maintain optimal C_{min} with every 4-week dosing for a 12-week treatment period, with the exact dose determined based on emerging data during the course of the study. The dose was expected to be in the range of 100 to 250 mg.

[0242] All doses were anticipated to be safe and well-tolerated based on nonclinical toxicology and Phase 1a SAD healthy volunteer data, in which doses up to 250 mg SC were safe and well tolerated with no dose-related safety findings.

[0243] Results from this study were anticipated to support future studies for the treatment of TED.

[0244] Cohort 1 provides low-dose safety information with a 6-week treatment duration. Cohorts 2 and 3 were designed to provide a treatment duration that may differentiate the dose levels, as emerging data from anti-IGF-1R therapies suggests 6 weeks may not be sufficient for this purpose. Additionally, based on data from other anti-IGF-1R therapies, it was believed an open label design for Cohorts 2 and 3 would provide sufficient data in this early-stage study to support subsequent clinical studies. Based on a preexisting decision tree in the study protocol, as explained herein, Cohort 4 was added to provide high-dose safety and efficacy information based upon emerging data from Cohorts 1-3.

[0245] Details of the study protocol are set forth below.

Study Objectives and Endpoints

Primary Objective

[0246] The primary objective of this study is to evaluate the safety and tolerability of multiple doses and multiple-dose regimens of lonigutamab when administered as SC injections in subjects with TED.

Secondary Objective

[0247] The secondary objective is to characterize the pharmacokinetic (PK) of lonigutamab in TED patients after SC administration.

Exploratory Objectives

[0248] The exploratory objectives of this study are: (i) evaluate the effect of lonigutamab on the proptosis responder rate over time; (ii) evaluate the effect of lonigutamab on the change in proptosis measurement in the study eye over time; (iii) evaluate the effect of lonigutamab on the diplopia responder rate over time; (iv) evaluate the effect of lonigutamab on diplopia score over time; (v) evaluate the effect of lonigutamab on the change in the Clinical Activity Score (CAS) over time; (vi) evaluate the effect of lonigutamab on the change in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire score including overall score and subscale scores over time; (vii) evaluate pharmacodynamic (PD) biomarkers (serum IGF-1 levels and PBMC-RO) of lonigutamab over time; (viii) evaluate changes in lid retraction; and (ix) evaluate the immunogenicity of lonigutamab in TED patients after SC administration.

Primary Endpoint

[0249] The primary endpoint of this study is to assess the incidence and characterization of serious and nonserious TEAEs.

Secondary Endpoint

[0250] The secondary endpoint of this study is to characterize the PK, to include, but not limited to, C_{max} and C_{min} of lonigutamab, as data allow.

Exploratory Endpoints

[0251] The exploratory endpoints of this study are: (1) Proptosis responder rate (the percentage of subjects with a ≥2 mm reduction from Baseline/Day 1 in the study eye without deterioration [≥2 mm increase] of proptosis in the fellow eye) over time; (2) Mean change in proptosis measurement in the study eye over time; (4) Diplopia responder rate (percentage of subjects with baseline diplopia >0 who have a reduction of ≥1 grade over time; (5) Mean change in diplopia score over time; (6) Mean change in CAS over time; (7) Mean change in the GO-QoL questionnaire overall and subscale scores over time; (8) Mean change in blood pharmacodynamic biomarkers over time; (9) Change in lid retraction using marginal reflex distance measurements over time; and (1) Proportion of subjects that develop ADAs after administration of multiple doses of lonigutamab over time.

Investigational Plan

Description of Overall Study Design and Plan

[0252] This Phase 1/2, multicenter, adaptive, multiple dose-ranging clinical study is designed to evaluate lonigutamab in subjects with TED.

[0253] The study has 3 different periods:

Cohort 1:

Screening Period: Day -28 to Day -1
Treatment Period: Day 1 to Day 21

Follow-up Period: Day 22 to Day 113

Cohorts 2 and 3:

Screening Period: Day -28 to Day -1
Treatment Period: Day 1 to Day 85

Follow-up Period: Day 86 to Day 169

Cohort 4

Screening Period: Day -28 to Day -1

Treatment Period: Day 1 to Day 84

Follow-up Period: Day 85 to Day 169

Screening Period:

[0254] At Screening, after subjects provide informed consent, Screening assessments specified in this protocol are performed to determine eligibility to enroll in this study. Individuals who sign the informed consent form to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria may be rescreened in accordance with the protocol as set forth herein.

Treatment Period

[0255] The study's plan includes 4 cohorts, which are summarized as follows:

[0256] Cohort 1: Double-masked, randomized 3:1 to lonigutamab (40 mg once every 3 weeks [Q3W] SC) or matching placebo for 2 doses. Up to approximately 8 subjects planned.

[0257] Cohort 2: Open-label lonigutamab at an initial loading dose of 50 mg of lonigutamab followed by 11 weekly (QW) doses of 25 mg of lonigutamab. Cohort 2 opened once at least 4 subjects had been dosed in Cohort 1.

[0258] Cohort 3: Open-label lonigutamab (50 mg Q4W SC) for 3 doses enroll up to approximately 15 subjects. The exact dose is determined based on emerging data and was expected to be in the range of 100 to 250 mg. Cohort 3 opened once at least 2 subjects had been dosed in Cohort 2.

[0259] Cohort 4: Open-label lonigutamab (TBD 70 mg at Q3W/Q4W dose) at a higher 70 mg dose that enrolls approximately 8 subjects. The dose should maintain lonigutamab levels > 1.5 μg/mL, allowing full receptor saturation and reducing the risk of target mediated drug disposition. This cohort was added based on data from Cohorts 1-3. The treatment period is scheduled to last 12 weeks, after which there is a 12 week post-treatment follow-up period.

Follow-up Period:

[0260] Subjects are followed up for up to 13 weeks after the Treatment Period for the assessments outlined in the Schedules of Assessments set forth in Table 1, Table 2, Table 3, Table 4, and Table 5.

End-of-Study

[0261] A subject has fulfilled the requirements for study completion when the subject has completed all study periods, including the End-of-Study Visit as indicated in the Schedules of

Assessments (Table 1, Table 2, Table 3, Table 4, and Table 5). The end of the study is the subject's last scheduled visit/assessment as indicated in the Schedule of Assessments (Table 1, Table 2, Table 3, Table 4, and Table 5).

Study Subject Inclusion/Exclusion Criteria

[0262] Subjects must meet all of the inclusion criteria set forth in Table B to be included in the study. Subjects meeting any of the exclusion criteria at Screening or Baseline/Day 1, as set forth in Table B, are ineligible to participate in this study.

Table B

Subject Inclusion Criteria

1. Willing and able to sign an informed consent form (ICF), understand all study requirements, and be willing to comply with them for the duration of the study.
2. Male or female, ≥18 and ≤75 years of age at the time of consent.
3. Proptosis defined in the study eye as ≥3 mm above normal based on race and sex in the judgement of the investigator. The study eye is defined as the more severely affected eye. If both are equally affected, the right eye will be designated as the study eye.
4. Clinical diagnosis of Graves' disease with active TED and a CAS ≥4 (using a 7-item scale) for the most severely affected eye at Screening and Baseline/Day 1.
5. Onset of active TED symptoms (as determined by subject records) within 24 months before Baseline/Day 1.
6. Subjects 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.
7. Contraceptive barrier requirements:

If female, meets one of the following requirements:

a. Is of childbearing potential and agrees to use at least 1 low user dependent highly effective method of contraception OR 1 user dependent highly effective method of contraception combined with an additional effective barrier method from at least 28 days prior to the first study drug dose through to at least 180 days after study drug administration.

It is the participant's responsibility to notify the Investigator if a pregnancy occurs from the end of their study participation until 180 days after study drug administration.

OR:

b. Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal ligation), or is in a postmenopausal state (i.e., at least 1 year without menses and without an alternative medical condition prior to the Screening visit).

If male, meets one of the following criteria:

a. Abstinence from penile vaginal intercourse as their usual and preferred lifestyle from screening to 180 days post dose.

b. Unable to procreate, defined by surgically sterile (i.e., has undergone a vasectomy with documented azoospermia as defined in Appendix 1)

c. Agrees to refrain from donating semen and use male condom (and should also be advised of the benefit for a female partner to use highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential from at least 28 days prior to the first study drug dose through to at least 180 days after study drug administration. Highly effective contraceptive methods are defined in Appendix 1.

Note: During the study intervention period and for at least 180 days after the last dose of study intervention, the Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

8. If a WOCBP, subject should have a negative pregnancy test result at Screening and Baseline/Day 1 visits.

Subject Exclusion Criteria

1. History or evidence of any clinically significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator, may pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.

2. Pathology related to irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD):

a. Established diagnosis of IBS for 2 or more years prior to screening,

OR

b. Any history or current confirmed diagnosis of IBD,

OR

c. Signs and symptoms: any of the following symptoms (of unknown etiology) OR any signs or symptoms within the last year that in the opinion of the Investigator may be suggestive of IBD should be screened for the symptoms below.

If the history is positive, the subject should receive a fecal calprotectin test. If fecal calprotectin test is required, subjects with values ≥ 500 µg/g should be excluded:

(i) Prolonged or recurrent diarrhea with or without

blood

(ii) Prolonged or recurrent abdominal pain

(iii)Blood in stool

3. Pathology related to hearing:

a. Current tinnitus continuously experienced over the last month prior to screening

OR

b. Documented autophony

OR

c. Documented clinically significant hearing loss

OR

d. Audiology showing:

i. For tested frequencies up to 2000 Hz (inclusive): any hearing impairment (> approximately 26 dB)

ii. For frequencies above 2000 Hz:

- Subjects <45 years of age, hearing impairment > approximately 41 dB (mild hearing loss)
- Subjects 45 years or older, hearing impairment > approximately 56 dB (moderate hearing loss)

4. Decreased best corrected visual acuity within 6 months of screening due to optic neuropathy as defined by a decrease in vision of 2 lines of Snellen chart in subjects with available prior Snellen chart exams. If prior Snellen exams not available, symptoms of optic neuropathy such as defective color vision, a relative afferent pupillary defect (RAPD), or an abnormal optic disc appearance should lead to an appropriate evaluation to exclude optic neuropathy.

5. Corneal decompensation unresponsive to medical management.

6. Decrease in CAS ≥2 points (using a 7-item scale) in the study eye between Screening and Baseline/Day 1.

7. Decrease in proptosis of ≥2 mm in the study eye between Screening and Baseline/Day 1.

8. Previous orbital irradiation (for any cause) or any previous surgical treatment for TED.

9. Requires immediate surgical ophthalmological intervention and is planning corrective surgery/irradiation during the course of the study (cataract surgery permitted).

10. Alanine aminotransferase or aspartate aminotransferase >2.5 × the upper limit of normal or serum creatinine >2 × the upper limit of normal according to age at Screening.

11. Subjects with diabetes or glycated hemoglobin A1c (HbA1c) >6.0% at screening (a history of gestational diabetes is allowed).

12. Use of:

- Homeopathic or nonpharmaceutical thyroid medications or supplements as a primary or complementary therapy unless discontinued at least 2 weeks prior to Baseline/Day 1.
- Steroids as follows:
  - Any steroid use (IV or oral) with a cumulative dose equivalent to >3 g of methylprednisolone for the treatment of TED within the last year.
  - Previous steroid use (IV or oral) specifically for the treatment of TED not to exceed 1 g total dose in the 8 weeks prior to Screening.
  - Any steroid use (IV or oral) within 4 weeks prior to Screening.
  - Previous use of steroid eye drops is allowed if discontinued at least 4 weeks before Screening.
- Corticosteroid use for conditions other than TED within 4 weeks before Screening:
  - Nonophthalmic indications within 4 weeks before Screening (topical steroids for dermatological conditions, intra-articular joint injections, and inhaled steroids for asthma are allowed).
  - Ophthalmic indications within 6 weeks before Screening, including periocular and topical steroids, sub-Tenon's Kenalog injections and intravitreal injections.
- Selenium and biotin must be discontinued 3 weeks before Screening and must not be restarted during the study; however, taking a multivitamin that includes selenium and/or biotin is allowed.
- Previous use of teprotumumab or any other IGF-1R inhibitor.

- Any previous treatment with a biologic drug for the treatment of TED (e.g., rituximab and tocilizumab).
- Any other immunosuppressive agent within 1 month before Screening.
- Investigational agent for any condition within 60 days before Screening or anticipated use during the course of the trial.
- Individuals who have been exposed within the last 2 years prior to Screening to antimalarials such as quinine, platinum-based chemotherapies, such as cisplatin or carboplatin, and/or aminoglycoside antibiotics, such as gentamycin or tobramycin.

13. Identified another preexisting ophthalmic disease that, in the opinion of the investigator, would preclude study participation or complicate interpretation of study results.

14. Received live vaccination 2 months prior to dosing or scheduled to receive a live vaccine during the course of the study.

15. Currently a smoker, smoking more than 10 cigarettes per day.

16. Bleeding diathesis that, in the opinion of the investigator, would preclude inclusion in the clinical trial.

17. Malignant condition in the past 60 months (except successfully treated basal/squamous cell carcinoma of the skin).

18. Known hypersensitivity to any of the components of lonigutamab or previous hypersensitivity reactions to any mAb.

19. Any other condition that, in the opinion of the investigator, would preclude inclusion in the study.

20. At Screening:

a. Positive test for human immunodeficiency virus (HIV) antibodies

b. OR positive hepatitis B surface antigen (HBsAg)

c. OR positive hepatitis B core antibodies (HBcAb)/Hepatitis B surface antibodies (HBsAb) with positive hepatitis B virus deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) reflex test

d. OR positive Hepatitis C virus (HCV) antibody test

e. OR positive QuantiFERON tuberculosis (TB) test OR if subject does not have a negative QuantiFERON test and if any one of the following are true:

- Subject has symptoms consistent with TB as determined by the investigator
- Subject has historical exposure to TB

- Subject has lived outside of the USA, Canada, New Zealand, Australia, or Western Europe for more than 6 months
- Subject has been vaccinated against TB.

21. Females who are pregnant, lactating, or planning on becoming pregnant in the next 12 months.

22. Clinically significant electrocardiogram (ECG) findings unless approved by Cardiologist or Study Medical Monitor.

23. Previously enrolled or withdrawn from this study.

24. Active substance abuse (drug or alcohol) within 24 weeks prior to first dose of study drug, as determined by the investigator.

25. Any condition that compromises the ability of the subject to give written informed consent and/or subject's unwillingness or inability to comply with study protocol.

Life-Style Considerations

[0263] The protocols requires subjects to limit alcohol consumption to <2 per day, and <7 alcoholic drinks per week. An alcoholic drink is defined as a 6 oz (175 mL) glass of wine, a 1 oz (30 mL) glass of hard liquor (e.g., whiskey), or an 8 oz (250 mL) glass of beer. Subjects should avoid exposure to loud noises during the course of the study, such as, but not limited to, concerts, headphone use, shooting ranges, work on construction sites without proper ear protection, motorcycles, etc.

Rescreening

[0264] Participants who sign the ICF to participate in the study, but who did not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore did not enroll in the study (screen failures), may be rescreened upon consultation with the Medical Monitor. Such individuals may be allowed to rescreen up to 1 time, unless approved by the Medical Monitor.

Discontinuation of Study Drug

[0265] In rare instances, it may be necessary for a subject to permanently discontinue study drug. The reason for permanent discontinuation of study drug will be documented. If study drug is

permanently discontinued, the subject will be encouraged to remain in the study to be evaluated for safety and efficacy. Subjects continue to complete study assessments as outlined in the Schedule of Assessments where possible, with the exception of study drug administration. Reasons for discontinuation from study drug include any of the following: Subject request; Death; Lost to follow up; Emergency unblinding (Cohort 1 only); Liver chemistry stopping criteria; AE/SAE; Subject becomes pregnant while on study drug; and Subject is non-compliant with study procedures that would put the subject at risk for continued participation in the trial as determined by the Investigator or Medical Monitor.

[0266] Further, subjects with newly diagnosed IBD during the study must: discontinue study drug and be followed-up until resolution of active IBD symptoms; and be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist.

[0267] Further, if the subject has a clinical laboratory value meeting any of the following criteria, study drug must be interrupted. The laboratory test must be repeated in 1 to 2 weeks at a scheduled or unscheduled visit. The option to restart study drug after interruption, if felt warranted by the Investigator, should be discussed with, and cannot be implemented before agreement from, the Medical Monitor:

- Neutrophil count $<1.0 \times 10^9$/L
- Platelets $<50{,}000/mm^3$
- Hemoglobin <8.5 g/dL with decrease of at least 2 g/dL from Baseline
- Creatinine >2 × Baseline
- Any other laboratory abnormality that in the Investigator's judgement could indicate a medical condition that puts the subject's safety at risk and that do not respond to standard medical interventions (e.g., hyperkalemia) or do not resolve spontaneously.

[0268] If sponsor medical monitor approval to restart study drug after interruption is not granted, then the subject must permanently discontinue study drug and may continue in the study for protocol specified study assessments. .

Liver Chemistry Stopping Criteria

[0269] Discontinuation of study drug for abnormal liver tests is required by the investigator when a subject meets 1 of the conditions outlined in the algorithm or in the presence of abnormal liver

chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in the best interest of the subject (FIG. 6). The investigator may consider rechallenge if a reasonable alternative explanation is identified, liver tests have returned to baseline levels, and after consultation with the medical monitor.

[0270] Study drug restart/rechallenge after liver chemistry stopping criteria are met may be allowed in this study. If the subject meets liver chemistry stopping criteria, do not restart/rechallenge the subject with study drug unless: Sponsor Medical Monitor approval is granted, independent ethics committee (IEC) and/or institutional review board (IRB) approval is obtained, if required. If study drug is interrupted for suspected study drug-induced liver injury, the subject should be informed of the risk of death, liver transplantation, hospitalization, and jaundice before resumption of dosing. If sponsor Medical Monitor approval to restart/rechallenge the subject with study drug is not granted, then the subject must permanently discontinue study drug and may continue in the study for protocol-specified study assessments.

Subject Discontinuation/Withdrawal from Study

[0271] If a subject is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Subjects who complete or discontinue early from the study will be asked to return to the study site for the End-of-Study (EOS) Visit to complete assessments as indicated in the Schedule of Assessments (Table 1, Table 3, and Table 4). Subjects who discontinue treatment will be encouraged to continue with other study assessments as scheduled until End of Study.

[0272] In the event that a subject discontinues prematurely from the study because of a TEAE or serious TEAE, the TEAE or serious TEAE will be followed up with until it resolves (returns to normal or baseline values), or stabilizes, or until it is judged by the investigator to no longer be clinically significant, or the subject is lost to follow-up.

[0273] Once a subject is withdrawn from the study, the subject may not re-enter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Subject withdrawal of consent: At any time, a subject's participation in the study may be terminated at the subject's request
- Decision by the Sponsor

- Decision by the Investigator (following discussion with the sponsor)
- Lost to follow up

Withdrawal of consent

[0274] A subject may withdraw from the study at any time without jeopardizing subsequent medical care. At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Assessments. See the Schedule of Assessments for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The subject will be permanently discontinued from the study drug and the study at that time. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and notify the sponsor or its designee.

Lost to Follow Up

[0275] A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions are taken if a subject fails to return to the clinic for a required study visit:

[0276] (i) The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

[0277] (ii) Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 attempts at known effective points of contact [e.g., phone, e-mail, text], and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

[0278] (iii) Should the subject continue to be unreachable, he/she will be considered lost to follow-up.

[0279] Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

[0280] Should a study subject experience a serious or severe temporal reaction after administration of study drug, dosing of additional subjects may be temporarily suspended and a Safety Review Committee meeting will be promptly scheduled to review the subject's status and all available safety data.

Treatments

Details of Study Treatments

[0281] The test product, lonigutamab, is an anti-IGF-1R mAb. Lonigutamab drug product is formulated in 2 concentrations, 20 mg/mL and 125 mg/mL. The 20 mg/mL concentration is in 25 mM histidine with 6% sucrose at pH 6.0. The drug product is colorless to a pale yellow and slightly opalescent. The 125 mg/mL concentration is in 25 mM histidine with 5% D sorbitol at pH 6.0. The drug product is a pale yellow to yellow and slightly opalescent. The study drug is administered via SC route.

[0282] The matching placebo is a solution without the active component and appears clear and colorless.

[0283] Study drugs are provided in cartons containing 1 glass vial. Each vial will be labeled with the drug identification, strength, volume, and other information required by local regulations. Each carton contains the study drug identification number, the name and address of the Sponsor, and any other information required by local regulations.

[0284] Lonigutamab or placebo is administered as a SC injection to the clean periumbilical area or upper thigh by the investigator or qualified medical professional under the supervision of the investigator when administered in the clinic.

[0285] For Cohort 2, dosing for select administrations may be administered in the subject's home by a home health nurse, as outlined in the Schedule of Assessments Table 3.

[0286] The date and time each dose is administered and the injection site is recorded in the source data and eCRF for each study subject.

[0287] A record of the quantity of study drug dispensed and administered to each subject is maintained and reconciled with study drug and compliance records. Dosing date, including study drug delays are also be recorded. Partial dose administration will be explained.

[0288] Subjects are dosed within the window as detailed in the Schedules of Assessments unless approved by sponsor Medical Monitor.

[0289] All missed or delayed doses are documented. If the investigator determines a subject should not be dosed within the protocol-defined window for a safety reason, the subject must permanently discontinue from treatment, unless approved by sponsor Medical Monitor.

[0290] Visit/dosing windows of ±2 days on either side of the scheduled visits/dosing are applicable, unless approved by sponsor Medical Monitor.

[0291] The study drugs are stored in a refrigerator at 2 °C to 8 °C. For any Cohort 2 subjects being administered study drug at home by a home health nurse, the study drug is dispensed to the subject during a clinic visit with detailed instructions on transportation and storage of study drug. These subjects are also required to bring back all used and unused vials back to the site for study drug reconciliation.

[0292] Detailed instructions for study drug dispensing and injection are included in the pharmacy manual.

Dosage Schedule

[0293] Cohort 1 is a randomized, double-masked dosing group. Cohorts 2, 3, and 4 are open-label. The designated site representative prepares the study drugs on the day of treatment, or, for Cohort 2, subjects may be given the option to have certain scheduled visits at their home with a home health nurse, who prepares and administers study drug.

Method of Study Treatment Assignment

[0294] For Cohort 1, at the Baseline Visit (Day 1), a subject who qualifies to participate in the study is centrally randomized in an approximate 3:1 ratio using a computerized interactive voice and web response system (IWRS) to receive either lonigutamab or placebo.

[0295] Cohort 2 opened once 4 subjects had been dosed in Cohort 1. When Cohort 2 was opened, Cohort 1 was closed. All subjects enrolled into Cohort 2 received the same treatment.

[0296] Cohort 3 opened once 2 subjects had been dosed in Cohort 2. When Cohort 3 is opened, Cohort 2 is closed. All subjects enrolled into Cohort 3 received the same treatment. Cohort 4 is opened based upon emerging data from Cohorts 1-3. All subjects in Cohort 4 receive the same treatment.

[0297] The sponsor may open or close a cohort based on emerging data once the minimum number of subjects is enrolled (only one cohort is open at the time).

[0298] For each subject, the sites receive the appropriate carton number to be dispensed from the IWRS.

[0299] Each subject in all cohorts receives a unique subject ID number by IWRS at the Screening visit, which will be identifiable throughout the study.

Masking

[0300] Cohort 1 is a randomized, double-masked dosing group. The investigators, site staff assessing the safety and efficacy, other related study staff (including the contract research organization and Sponsor), all subjects, and central laboratories will remain masked to the study treatment assignment until the last subject in this cohort completes their last visit, after which study treatment assignment is unmasked. All staff performing evaluation of PK, PD, and immunogenicity assessments are regarded as unmasked.

[0301] According to the randomization schedule as indicated in the Schedule of Assessment (Table 1) and in accordance with the pharmacy manual, the investigator or designee obtains the study drug number from the IWRS for the subject, and the number is provided to the unmasked pharmacist or designee at the study center who is responsible for the preparation of study treatment. This unmasked assignee prepares the study treatment in accordance with the study drug number from the IWRS. Prepared study treatments are identical in appearance and labeled in a masked manner. No other study site personnel, subjects, Sponsor personnel, or Sponsor designees are unmasked to treatment assignment throughout the duration of the study unless unmasking is required in the event of an emergency. If an investigator becomes unmasked to a given subject's study treatment, that subject is discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Sponsor's medical monitor must be obtained in such instances. If a subject is discontinued because of unmasking, where possible, the end-of-study (EOS) assessments/procedures will be completed. Any AEs are followed until resolution.

[0302] In the event that emergency unmasking is required for a given subject because of SAEs or concerns for the subject's safety or wellbeing, the investigator may break the randomization code for the subject via the IWRS, by which system the unmasking will be captured. The investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. The unmasking and its cause are also be documented.

[0303] Communication between masked and unmasked staff is kept to a minimum. During the study, prior to final unmasking of the treatments after database lock, programming of PK, PD, and immunogenicity data is based on dummy data to ensure the masking remains.

[0304] Cohorts 2, 3, and 4 are open-label.

Treatment Accountability and Compliance

[0305] The pharmacist or other designated unmasked individual maintains records of study treatment delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records include dates, quantities, batch/serial numbers, expiration dates, in-clinic/pharmacy temperature log, and unique code numbers assigned to the product and study subjects.

[0306] Investigators maintain records that adequately document that the subjects were provided with the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product is not returned to the Sponsor until accountability has been fully monitored.

[0307] Additional details are described in the Pharmacy Manual.

Prior, Concomitant, and Prohibited Therapy

[0308] Restricted prior therapies are provided above.

[0309] All medications and treatments ever taken for Thyroid Eye Disease and any other medications and treatments taken in the last 6 months by or administered to the subject for the period before Screening and during the study are recorded in the eCRF.

[0310] Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study is recorded along with: reason for use; dates of administration including start and end dates; dosage information including route, dose, and frequency.

[0311] Prohibited medications while on study:

- Homeopathic or nonpharmaceutical thyroid medications or supplements as a primary or complementary therapy
- Any steroid use (IV or oral) with a cumulative dose equivalent to >1 g of methylprednisolone for the treatment of TED
- Selenium and biotin
- Teprotumumab or any other IGF-1R inhibitor
- Other treatment with a biologic drug for the treatment of TED (e.g., rituximab, tocilizumab) and other immunosuppressive agent
- Any other investigational agent
- Any platinum-based chemotherapies, such as cisplatin or carboplatin, and/or aminoglycoside antibiotics, such as gentamycin or tobramycin.

- Antimalarials such as quinine.
- Loop diuretics such as furosemide, bumetanide, or ethacrynic acid (unless approved by Medical Monitor)
- Immunization with a live or live attenuated vaccine should be avoided within 2 months prior to dosing and throughout the study. If any vaccination is contemplated, it must first be discussed between the Medical Monitor and the investigator. All medications taken by subjects after Screening until the last study day will be documented as concomitant medications. The entry may include the dose, indication, and dates of use.

Study Procedures

[0312] Schedules of Assessments Table 1, Table 3, and Table 4 outline the timing of procedures and assessments performed throughout the study for Cohorts 1, 2, and 3, respectively. Additional Pharmacokinetic and Pharmacodynamic Sampling Schedules Table 2 and Table 5 outline the timing of PK, and PD sample collection in addition to those contained in the Schedules of Assessments. The present disclosure also specifies laboratory assessment samples obtained. Cohort 4 will use a protocol, procedures, schedule, and assessments based on that of Cohort 3, in which the dose is changed to 70 mg QW3/QW4 for 12 weeks.

Efficacy Assessments

[0313] The Schedules of Assessments (Table 1, Table 3, and Table 4) outlines the efficacy assessments performed throughout the study and their timing.

[0314] Efficacy assessment are performed for both eyes at each assessment time point. The most significant proptosis is defined as the "study eye" at the Baseline/Day 1 Visit. If both are equally affected, the right eye is designated as the study eye.

[0315] The same observer conducts all ophthalmic exams for the same subject throughout the duration of the study and within the specified visit window unless approved by the sponsor Medical Monitor.

Clinical Measures of Thyroid Eye Disease

Proptosis (Exophthalmos)

[0316] Proptosis assessments are performed using a Hertel exophthalmometer provided by the Sponsor for consistency in measurement, and (except when strictly unavoidable) the same Hertel instrument and same observer is used at each evaluation for the full duration of the study. Additionally, the same intercanthal distance is used on each occasion. Instructions for the measurement of proptosis are included in the Study Procedures Manual.

[0317] Subjects who have a ≥2 mm decrease in proptosis from Screening to Baseline/Day 1 in the study eye are not eligible for randomization.

Diplopia

[0318] Diplopia is assessed using the Gorman scale (0-3) resulting in one of the following assessments: None =0, With Gaze = 1, Intermittent = 2 and Constant = 3.

Clinical Activity Score (CAS)

[0319] The CAS measures the classical signs of acute inflammation (pain, redness, swelling, and impaired function) in Graves' ophthalmopathy.[10,11] One point is given for the presence of each of the parameters assessed. The sum of all points defines clinical activity: active Graves' ophthalmopathy if the score is ≥4 using a 7-item scale.

[0320] CAS is administered to the subject at the time points indicated in the Schedules of

[0321] Assessment (Table 1 Table 3, and Table 4). The CAS must be ≥4 at the time of Screening and Baseline/Day 1. Subjects whose CAS score decreases 2 or more points from Screening to Baseline/Day 1 are not eligible for Randomization. *Graves' Ophthalmopathy Quality of Life* The GO-QoL is a patient-reported questionnaire designed to assess how their Graves' ophthalmopathy affects different aspects related to quality of life (visual functioning and psychosocial consequences).[12] There are 16 items that are graded on a 3-point Likert scale. The points given to questions 1-8 and 9-16 are added to obtain 2 raw scores ranging from 8 to 24; one for visual functioning and one for appearance. The GO-QoL questionnaire will be completed at the time points indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4). See FIG. 7 for the assessment details.

Facial Photos

[0322] Facial photos are taken at the time points indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4). These photos are transferred to a central reader masked to image sequence, cohort assignment, and study drug randomization (as applicable).

Safety Assessments

[0323] Safety is assessed via AE and concomitant medication use monitoring, physical and ophthalmic examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry [including HbA1c], and urinalysis), pregnancy testing (if applicable), ECGs, and audiology (if applicable). Protocol-specified visits are specified in the Schedules of Assessments (Table 1, Table 3, and Table 4).

[0324] Clinical safety laboratory evaluations include investigator review of the laboratory report, documenting this review, and recording any clinically significant changes occurring during the study as an AE. The laboratory reports are filed with the source documents.

[0325] Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

[0326] If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Medical History

[0327] Medical history is recorded at Screening. Investigators document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all prior significant illnesses. Additional preexisting conditions present at the time when informed consent is given and up to the time of first dosing (Baseline/Day 1; Visit 1) are regarded as concomitant. Medical history includes alcohol consumption and smoking history.

[0328] Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are documented as AEs on the eCRF. All changes which do not present at baseline or described in the past medical history and identified as clinically noteworthy are recorded as AEs.

[0329] Additionally, demographic data is collected for all subjects and include year of birth or age according to applicable regulations, sex, and ethnicity.

Vital Signs and Body Measurements

[0330] Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) are evaluated at the visits indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4). All vital signs are measured after the subject has been resting for at least 5 minutes. Blood pressure measurements are taken in the same arm for the duration of the study. Body weight (without shoes) and height (without shoes) are recorded at Screening, with body weight repeated as denoted in the Schedule of Assessments (Table 1, Table 3, and Table 4).

[0331] Vital sign measurements is repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements are repeated at the investigator's discretion. Any confirmed, clinically significant vital sign measurements are recorded as AEs.

Physical Examination

[0332] A complete physical examination (head and neck, eyes, ears, nose, mouth, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) is performed at Screening and at Day 113 (Cohort 1) or Day 169 (Cohorts 2 and 3). Physical examinations are performed by qualified, trained medical personnel.

[0333] A symptom-based physical examination is performed at the visits indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4). Symptom-driven, limited physical examinations are performed as clinically indicated at any study visit.

Ophthalmic Examination for Safety

[0334] In addition to the ophthalmic examinations conducted for efficacy other assessments are performed at the visits indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4), including visual acuity, a non-dilated slit lamp evaluation, and measurements of intraocular pressure.

Electrocardiograms

[0335] A 12-lead, resting ECG is obtained at the visits indicated in the Schedules of Assessments (Table 1, Table 3, and Table 4). The subject is rested quietly for 5 minutes in supine position before the ECG recording.

[0336] An assessment of normal or abnormal is recorded; if the ECG is considered abnormal, the abnormality is documented on the eCRF. ECGs are repeated if clinically significant abnormalities are observed, or artifacts are present.

Audiology

[0337] Audiology testing is performed according to the Schedule of Events (Table 1, Table 3, and Table 4) and for any cases of suspected hearing impairment (including hearing loss) self-reported by study subjects during the course of the study. Any hearing related changes meeting the definition of an AE are reported as an adverse event of special interest.

Audiology Safety: Stopping Criteria

[0338] Audiology stopping criteria are designed to assure subject safety and to guide when treatment discontinuation should be considered. The guidelines for changes in hearing level provided below are based on the American Speech-Language-Hearing Association (ASHA). Change in hearing sensitivity is always computed relative to baseline measures. According to

ASHA guidelines for the Audiologic Management of Individuals Receiving Cochleotoxic Drug Therapy[13], criteria to indicate hearing decrease during audiological monitoring are defined as:

- 20 dB decrease at any one test frequency, OR
- 10 dB decrease at any two adjacent test frequencies, OR
- loss of response at three consecutive test frequencies where responses were previously obtained

[0339] If a study subject meets any of these criteria, the change from baseline are confirmed by repeat testing. If the repeat testing procedure is confirmative, treatment discontinuation and further ontological follow-up (including audiology) is warranted. Subjects continue to complete study assessments as outlined in the Schedule of Assessments where possible, with the exception of study drug administration.

Liver Safety: Actions and Follow-up Assessments and Study drug

Restart/Rechallenge Guidelines

[0340] Phase 1 liver chemistry stopping criteria are designed to assure subject safety and to evaluate liver event etiology. The guidelines provided below (Table 6) are based on the EASL Clinical Practice Guidelines: Drug Induced Liver Injury (2019) and Food and Drug Administration 2009 Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation.

Laboratory Assessments

[0341] Laboratory assessment samples (Table 7) are to be obtained at designated visits as detailed in the Schedules of Assessments (Table 1, Table 3, and Table 4).

[0342] All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit.

Adverse Events

[0343] An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug.

[0344] NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

[0345] Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, audiology, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se is not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent.

[0346] Lack of efficacy or failure of expected pharmacological action per se is not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy is reported as AE or SAE if they fulfill the definition of an AE or SAE

[0347] Events NOT Meeting the AE Definition:

- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the first dose of study drug that do not worsen; such events should be recorded in the medical history eCRF
- Specific findings of worsening for TED-related symptoms (disease progression) are not recorded as AEs. Events, which are unequivocally due to disease progression, should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug. All other ophthalmic findings that are new or worsening are be recorded as AEs
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

[0348] Adverse events are reported by the subject (or, when appropriate, by a care giver).

[0349] The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The investigator is responsible for following up all AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug.

[0350] Subjects are instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached. Care is taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

[0351] Each AE is documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is classified as being serious or nonserious.

[0352] For the purposes of this study, the period of observation for collection of AEs extends from the time the subject is administered study drug until the EOS follow-up visit. Follow up of the AE, even after the date of therapy discontinuation, is required if the AE persists, until the event resolves or stabilizes at a level acceptable to the investigator.

Adverse Events of Special Interest

[0353] An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring can be appropriate.

[0354] AESI for this study include the following:

- Hyperglycemia meeting the definition of an AE
- Development of IBD
- Auditory changes

[0355] For any cases of hearing impairment (including hearing loss) reported by study subjects during the course of the study, appropriate follow-up and monitoring by audiology to assess the subject's hearing is warranted. Referral to otolaryngologist may be warranted, if in the opinion of the investigator further follow-up is required.

Time Period and Frequency for Collecting Adverse Event and Serious Adverse

[0356] All SAEs are collected from the signing of the ICF until the EOS follow-up visit at the timepoints specified in the Schedules of Assessments.

[0357] All AEs recollected from the first dose of study drug until the EOS follow-up visit at the timepoints specified in the Schedules of Assessments.

[0358] Medical occurrences that begin before the start of study drug but after obtaining informed consent are recorded as medical history/current medical conditions, not as AEs.

[0359] All SAEs are recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event. The investigator submits any updated SAE data to the sponsor within 24 hours of it being available.

[0360] Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor pharmacovigilance team.

Assessment of Severity

[0361] The investigator is responsible for assessing the severity for each AE and SAE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0):

- **Mild (Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)**: Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Severe (Grade 3)**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care

ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- **Life-threatening (Grade 4)**: Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)**: Events that result in death.

[0362] Many common AEs are able to be graded according to CTCAE. AEs that do not have a corresponding CTCAE term are assessed according to the general guidelines for grading used in CTCAE version 5.0 as stated above. Additional considerations when assessing severity are outlined below:

[0363] The seriousness of an AE should not be confused with its severity. Severity is a measure of intensity (e.g., Grades 1 through 5 or mild, moderate, severe, etc.), whereas seriousness is based on subject/event outcome as defined by the criteria in this protocol.

[0364] It is important to distinguish between category (AE versus SAE) and intensity (Grades 1 to 5) of AEs. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

[0365] An AE of severe intensity is not necessarily considered serious. For example, nausea that persists for several hours may be considered grade 3 nausea, but not an SAE. On the other hand, minor cardiac chest pain that results in hospitalization may be considered grade 1 but would be a SAE.

Assessment of Causality

[0366] The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgment in the assessment of causality according to the following categories:

- **Unrelated**: Another documented cause of the AE is most plausible; and/or the administration of study drug and occurrence of AE are not reasonably related in time; and/or causal relationship is considered biologically implausible.
- **Possibly related**: An event that follows a reasonable temporal sequence with study drug administration but could also be explained by other factors such as disease or other drugs.
- **Related**: There is clear evidence to suggest that the AE is more likely explained by the study drug and other possible contributing factors can be ruled out; a causal relationship is

clinically/biologically plausible, and there exists a plausible time sequence between onset of the AE and administration of the study drug.

[0367] Additional factors in the assessment of causality include the following:

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Serious Adverse Events

[0368] An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

- Results in death
- Is life-threatening
- The term life threatening in the definition of serious refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Results in inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse

Serious Adverse Event Reporting

[0369] SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Follow-up of AEs and SAEs

[0370] The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

[0371] If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

[0372] New or updated information are recorded in the originally submitted documents.

[0373] The investigator submits any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

Pregnancy

[0374] Details of all pregnancies after the start of study drug and until 180 days after the last dose of study drug in female subjects and, if indicated, female partners of male subjects are collected. If a pregnancy is reported, the investigator records pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of a pregnancy in a female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner, as applicable). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons is reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and are reported as such. The subject/pregnant female partner is followed to determine the outcome of the pregnancy. The investigator collects follow-up information on the subject/pregnant female partner and the neonate, and the information is forwarded to the sponsor or designee. Any poststudy pregnancy-related SAE considered reasonably related to the study drug by the investigator is reported to the sponsor or designee. While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, he/she may learn of an SAE through spontaneous reporting. Any female subject who becomes pregnant while participating in the study must discontinue study drug.

Overdose

[0375] An overdose is defined as administration of study drug given per administration or cumulatively which is above the maximum recommended dose according to the study protocol. Clinical judgement should always be applied. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (e.g., suicide attempt).

Pharmacokinetics

Pharmacokinetic Sampling

Blood Samples

[0376] Blood samples for PK analysis of serum lonigutamab levels are collected at the time points indicated in the Schedules of Assessments Table 1, Table 2, Table 3, Table 4, and Table 5. The actual date and time of each blood sample collection is recorded. The timing of PK samples may be altered, and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

[0377] Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a provided laboratory manual.

Pharmacokinetic Analytical Methodology

[0378] The concentration of study drug is determined from the serum samples using a validated analytical method. Details of the method validation and sample analysis are included with the final clinical study report.

Other Assessments

Pharmacodynamics

[0379] Blood samples for PD analysis of serum IGF-1 and PBMC-RO levels will be collected at the time points indicated in the Schedules of Assessments (Table 1, Table 2, Table 3, Table 4, and Table 5). The actual date and time of each blood sample collection will be recorded.

[0380] Details of PD blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

Immunogenicity

[0381] Immunogenicity will be assessed using a validated analytical method. The incidence of ADA will be determined at the time points indicated in the Schedules of Assessments Table 1, Table 2, Table 3, Table 4, and Table 5.

[0382] Details of immunogenicity blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

Statistical Analysis

[0383] A statistical analysis plan (SAP) including PK, PD, and ADA analysis will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will be finalized prior to performing any statistical analysis.

[0384] The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All subject data will be included in individual data listings, and summary tables will be provided. For continuous variables, data will be summarized using descriptive statistics including the number of subjects (n), mean, standard deviation, median, minimum, and maximum. For categorical variables, data will be tabulated with the number and proportion of subjects for each category.

[0385] The statistical summary will be presented by each treatment group and by the placebo group as applicable.

Determination of Sample Size

[0386] There is no formal sample size calculation as there is no formal statistical hypothesis to be tested. The sample size planned for the study arises from logistic feasibility and past experience with early-stage studies and available data from other anti-IGF-1R studies in TED. There are up to approximately 8 subjects in Cohort 1 and up to approximately 15 subjects in each of the remaining cohorts. Thus, up to approximately 38 subjects are to be enrolled in this study.

Analysis Populations

[0387] Full-Analysis Population/Safety Analysis Population - The full analysis and safety analysis population will include all subjects who are assigned or randomized to treatment groups and have at least 1 dose of study medication. This population will be used for the analysis of efficacy. Subjects will be analyzed by assigned or randomized treatment. The efficacy endpoints will be analyzed by the randomized treatment group whereas the safety endpoints will be analyzed by the actual treatment received.

[0388] PK Population - The PK population will include all subjects in the full analysis/safety analysis population who provide at least one measurable drug concentration value.

[0389] PD Population - The PD population will include all subjects in the full analysis/safety population who have at least one measurement of at least one PD marker.

[0390] ADA Population - The ADA population will include all subjects in the full analysis/safety population who have at least one measurement of ADA.

Safety and Tolerability Analysis

[0391] All reported AEs are coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number (percentage) of subjects who experienced TEAEs and the number of TEAEs (AEs with onset dates on or after the start of the study drug) reported are summarized by treatment group using system organ class (SOC) and preferred term (PT). Additional summaries present the number (percentage) of subjects with TEAEs and the number of TEAEs reported by severity and by relationship to study treatment; each subject is counted once per SOC/PT at the maximum severity or closest relationship to the study drug. Serious TEAEs are listed separately. Events with missing start dates are included as treatment-emergent. SAEs and AEs causing treatment discontinuation are tabulated. All AEs are listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

[0392] Original results and changes from Baseline/Day 1 are summarized using descriptive statistics for clinical laboratory parameters, vital signs, ophthalmic examination results, and ECG values by treatment group. Laboratory values are categorized as low/normal/high according to normal ranges, and shift tables versus Baseline/Day 1 will be created for each postbaseline visit. Laboratory abnormalities are also summarized. Physical examination testing results are summarized if appropriate.

[0393] Summary tables are provided for prior or concomitant medications initiated during the study period.

Efficacy Analysis

[0394] In general, all efficacy endpoints will be summarized descriptively. All efficacy summary and analysis will be presented by the randomized or assigned treatment group.

[0395] Analysis of Primary Efficacy Endpoint - Primary endpoint is safety and tolerability. Hence, there are no primary efficacy endpoints.

[0396] Analysis of Exploratory Efficacy Endpoints - The change from Baseline/Day 1 in proptosis measurement and CAS in the study eye will be summarized by treatment group and visit. The changes from Baseline/Day 1 in diplopia will be summarized by treatment group and visit. Change in marginal reflex distance measurements also will be summarized by treatment group and visit.

[0397] Pharmacokinetic Analysis - PK analysis will be performed on the PK population. Descriptive statistics for PK measurements will be provided, including the number of subjects, mean, geometric mean, standard deviation, coefficient of variation, min, max, and median.

[0398] Pharmacodynamic Analysis - PD analysis will be performed on PD population. Descriptive statistics for PD measurements will be provided, including the number of subjects, mean, geometric mean, standard deviation, coefficient of variation, min, max, and median.

Other Analyses

[0399] Immunogenicity Analysis - The number and percentage of subjects with ADA results will be presented by treatment group and visit.

[0400] Quality of Life - The original value and change from Baseline/Day 1 in the GO-QoL questionnaire overall and subscale scores will be summarized descriptively by treatment group and visit.

Preliminary Safety and Efficacy of Lonigutamab (Anti–IGF-1R) From a Phase 1/2 Clinical Study in Patients With Thyroid Eye Disease.

[0401] The following represent emergent data from the Phase 1/2 clinical study (NCT05683496), as outlined above, for patients with TED with Lonigutamab. As disclosed herein, based on the interim results from this trial, lonigutamab demonstrated rapid improvements in proptosis and clinical activity score (CAS) at the first measurement – within three weeks after the first subcutaneous dose.

[0402] This trial and disclosure details the first reported proof-of-concept results of a subcutaneous anti–IGF-1R in patients with TED. In the underlying clinical trial, patients achieved early clinical responses that were maintained over time, including at week 12 (off-treatment), supporting the potential for longer dosing intervals, as described with reference to Cohort 4 of the trial. As described herein, interim data from a first cohort of the study, Cohort 1, suggests lonigutamab was well tolerated and displayed clinical efficacy responses. This data has been further substantiated by interim data for a second cohort in the study.

[0403] FIG. 9A provides an overview of this multi-center Phase 1/2 clinical trial to evaluate the safety and efficacy of lonigutamab dosed subcutaneously. This figure outlines an earlier phase of the trial study, and describes collecting and analyzing data from the first two patient cohorts – Cohort 1 and Cohort 2. Eligible patients in the study are ≥18 to ≤75 years old and have active TED, with proptosis of ≥3 mm above normal range in the study eye and a Clinical Activity Score (CAS) of ≥4 (on a 7-item scale).

[0404] FIG. 10 provides the demographics and baseline characteristics of the patients in Cohort 1. The demographics and baseline characteristics in Cohort 1 were consistent with other TED studies and otherwise unremarkable.

[0405] Cohort 1 was double masked and randomized 3:1 to subcutaneous (SC) lonigutamab (40 mg every 3 weeks [Q3W]) or matching placebo for 2 doses to provide low-dose safety information.

[0406] In Cohort 1, 8 pts were enrolled (lonigutamab, n=6; placebo, n=2). FIG. 11A provides proptosis responses through the treatment period (week 6) and post-treatment period (week 12) in Cohort 1. As shown, 50% of patients in the lonigutamab group and 0/2 (0%) patients in the placebo group had a proptosis response (defined as a ≥ 2mm reduction in proptosis) at week 6 and week 12. FIG. 11B shows proptosis mean change during treatment period week 6 / off-treatment through week 12 for cohort 1. As shown in Fig. 11B, For patients of Cohort 1, the proptosis mean change (SD) from baseline was −2.2 (1.3) and −1.5 (1.8) at weeks 6 and 12 with lonigutamab (vs −1 and 0 for 1 placebo patient).

[0407] It should be noted that this is actually the registrational endpoint for TED because it is approximately the amount of bone that oculoplastic surgeons can scrape away from behind the eye before jeopardizing the brain in the attempt to reset the globe back into its orbit. It is known that patients often have much more than 2mm of proptosis – sometimes 10, 15 or even more than 20mm. Thus, the long-term dosing potential of lonigutamab indicates the ability to produce the depth and durability of response for patients with more severe proptosis. Remarkably in this cohort, even with the last dose being administered at 3 weeks, responses continue holding out to 12 weeks. This suggests a durability of effect that could factor into dosing decisions in the future.

[0408] The data for Cohort 1 further revealed that, among patients with baseline diplopia (lonigutamab, n=4; placebo, n=2), 1/4 (25%) lonigutamab vs 0% of placebo patients had a diplopia response at weeks 6 and 12.

[0409] FIG. 12 provides clinical activity scores (CAS) and changes from baseline at weeks 6 and 12 for Cohort 1. CAS, is another important measure of disease activity for TED, where patients are scored based on pain, redness and swelling around the eye. A ≥ 2-point reduction in CAS is considered a clinically meaningful improvement for patients. With lonigutamab, 6/6 (100%) patients achieved a ≥2-point CAS reduction (study eye) at weeks 6 and 12 vs 0% of placebo patients. Mean (SD) change in CAS from baseline for the study eye with lonigutamab was −3.5 at week 6 and −3.7 at week 12 (vs 0 and −1.0 in 1 placebo patient). As shown in the data provided in FIG. 12, there are rapid and deep responses, with 50% of patients receiving lonigutamab achieving a clinically meaningful reduction in CAS within 3 weeks and 100% within 6 weeks, which was maintained through 12 weeks. This efficacy stands in contrast to the results for patients receiving a placebo for which there has not been a CAS reduction detected.

[0410] FIG. 13 provides clinical activity score changes through week 12 and shows them in comparison to those of Tepezza IV and VRDN-001 IV. Ultimately the goal for patients with any chronic disease is resolution of all signs and symptoms to achieve as normal a life as possible. By treating TED like a chronic disease with longer term dosing, lonigutamab may provide transformative benefits. For TED, CAS of 0 or 1 is a hurdle that approximates achieving this transformative benefit to normalcy. As shown in the data provided in FIG. 13, CAS of 0 or 1 was achieved by 50% of patients by week 6. Based on all of these data it is believed that PoC has been demonstrated within this first cohort of treating TED patients subcutaneously with lonigutamab, with speed and magnitude of these responses at least comparable to the IV approaches.

[0411] Fig. 19 provides the results of GO-Quality of Life survey for cohort 1 starting from before treatment through the post-treatment period. The original value and change from Baseline/Day 1 in the GO-QoL questionnaire overall and subscale scores are summarized descriptively by treatment group and visit. As shown, the placebo group showed a marked decrease in GO-QOL score, whereas an improvement was seen during the treatment period for those receiving lonigutamab, which remained elevated relative to the starting value through the post-treatment period.

[0412] Thus, for Cohort 1, clinically meaningful improvements were seen in patients with evaluable diplopia at baseline, and no worsening in diplopia was seen in all patients on treatment.

[0413] Cohort 2 received lonigutamab with an initial loading dose of 50 mg, then 25 mg weekly (QW). FIG. 14 shows demographic and baseline characteristics for Cohort 2 of the clinical trial as outlined in FIG. 9A.

[0414] FIG. 15 shows proptosis responses and CAS responses for both Cohort 1 and Cohort 2 at week 6. In FIG. 15, depicted on the left, the line graph shows rapid improvement in proptosis response achieved by week 6 for 67% (4/6) of patients by week 4, the first assessment point, which is maintained through week 6. For these patients, at the week 6 assessment, the proptosis mean change (SD) from baseline was −1.8 (0.8). The middle bar chart shows clinically meaningful proptosis responses for both Cohorts 1 and 2 at the 6-week timepoint. Finally, on the right side, is an observe reduction in clinical activity scores, with 83% (5/6) of patients achieving a clinically meaningful (≥2 point) reduction in CAS (study eye) by week 6 for Cohort 2.

[0415] Further, for Cohort 2, in patients with baseline diplopia (n=5), 2/5 (40%) had a diplopia response to lonigutamab.

[0416] FIG. 20 shows the proptosis responses through week 12 for Cohort 2, which remained elevated relative to baseline through week 12 and at similar levels to those measured at week 6. . FIG. 21 shows proptosis mean change through week 12 for Cohort 2. For patients of Cohort 2, the proptosis mean change (SD) from baseline was −1.8 and −1.9 at weeks 6 and 12 with lonigutamab (vs −1 and 0 for 1 placebo patient).

[0417] FIG. 22 provides clinical activity scores (CAS) and changes from baseline at weeks 6 and 12 for Cohort 2. A ≥ 2-point reduction in CAS is considered a clinically meaningful improvement for patients. With lonigutamab, 6/6 (100%) patients achieved a ≥2-point CAS reduction (study eye) by week 12. Mean (SD) change in CAS from baseline for the study eye with lonigutamab was −2.3 at week 6 and −3.4 at week 12. FIG. 23 shows the CAS 0 or 1 through week 12 for Cohort 2, in which an improvement was seen between weeks 6 and 12.

[0418] FIG. 16A provides a comparison of diplopia responses observed in Cohort 1 and Cohort 2 compared with those seen in IV Teprotumumab IV studies. As shown, the responses observed in Cohort 1 and Cohort 2 are clinically meaningful. Fig. 16B shows the diplopia response through week 12 for patients of cohort 1 with baseline diplopia >0. One patient in the placebo group did not have any data. As shown, the diplopia response was maintained into the post-treatment period for those patients that showed improvement during the treatment period. FIG. 24 provides the

diplopia responses for patients of Cohort 2, which was maintained through week 12 in 50% of patients.

[0419] Fig. 25 provides the results of GO-Quality of Life survey for Cohort 2 starting from before treatment through week 12. The original value and change from Baseline/Day 1 in the GO-QoL questionnaire overall and subscale scores are summarized descriptively by treatment group and visit. As shown, an improvement was seen during the treatment period for those receiving lonigutamab, which continued to increase through week 12.

[0420] Based on these results, SC exposure with lonigutamab achieves a rapid and durable response, which enable optimization of the benefit/risk profile for treating patients with TED. Moreover, as shown in FIGS. 17A-17B, lonigutamab is able to achieve robust responses at a lower exposure relative to teprotumumab. As shown, in addition to establishing the clinical proof of concept with a favorable safety profile, observed exposures from Cohorts 1 and 2 are represented. Of note, the Y axis is a log scale. Of particular importance, are that the clinical responses achieved were at exposures below the C_{max} for teprotumumab, which is an important consideration for assessing the reduction of safety liabilities seen with IV administration of anti-IGF-1R treatments.

[0421] The 40mg Q3W dose results give confidence that lonigutamab may achieve monthly Q4W dosing in patients with TED. The durability of clinical responses out to 12 weeks further suggest the possibility of even less frequent dosing. Based on the results of this clinical trial, the exposure response relationship demonstrated provides the evidence needed to choose a dose to optimize efficacy while determining the potential to minimize safety risk.

[0422] FIG. 18 summarizes safety data obtained for Cohorts 1 and 2. As shown, in cohort 1, treatment-emergent adverse events (TEAEs) occurred in 4/6 (66.7%) patients receiving lonigutamab and 2/2 (100%) receiving placebo. Of the TEAEs, none were serious TEAEs, and all reported TEAEs were grade 2 or otherwise milder than grade 2. One patient in the placebo group discontinued (optic neuropathy).

[0423] In cohort 2, TEAEs were reported in 5/6 (83.3%) patients. Of the TEAEs, none were serious TEAEs, and all reported TEAEs were grade 2 or otherwise milder than grade 2.

[0424] For both Cohorts 1 and 2, the majority of TEAE events were mild, and did not lead to interruption in study drug administration except for the optic neuropathy recorded in one, discontinued placebo patient. For both cohorts, there was no hearing impairment, no hyperglycemia events, no serious adverse events and no deaths were reported among the patients.

Most common events (reported in 2 or more subjects on lonigutamab) were headache, injection site reactions, muscle spasms and tinnitus. Tinnitus was reported in 3 subjects, which in all cases was mild and resolved without intervention. Similarly, injection site reactions were all mild. Grade 2 events included headache, joint swelling, and nausea.

[0425] Thus, the experience to date demonstrates lonigutamab has been well-tolerated with a favorable safety profile.

[0426] The table below summarizes the an initial set of interim results for this Phase 1/2 Clinical Study in Patients with TED.

Endpoint	**Cohort 1**		**Cohort 2**
% of patients achieving response at 6 weeks	***Placebo (n=2)***	Lonigutamab 40mg Q3W (n=6)	Lonigutamab 50mg Loading Dose, 25 mg (QW) (n=6)
Proptosis Response (≥2 millimeter reduction in proptosis from baseline)	0%	50%	67%
CAS Response (≥ 2 point reduction in CAS)	0%	100%	83%
Diplopia Response (≥ 1 Bahn-Gorman improvement [1])	0%	25%	40%
Clinically meaningful response across each measure.			

[0427] As these results demonstrate, lonigutamab has been well-tolerated across in patients with active TED. Importantly, there have been no reports of hyperglycemia, hearing impairment, or serious adverse events. The results and data disclosed herein, demonstrate the results of subcutaneous administration of lonigutamab, which provides a clinically meaningful response in patients as early as 3 weeks after a single subcutaneous dose of lonigutamab. In addition, it appears that the safety profile of medication through the subcutaneous route is favorable relative to the standard of care and/or prior therapies utilizing the anti-IGF-1R mechanism. Further, given the growing body of evidence that suggests thyroid eye disease may have long-term sequelae, the convenience of a subcutaneous administered medication with a potentially favorable side effect profile, such as lonigutamab as disclosed herein, proves invaluable.

[0428] Thus, these interim results of the clinical trial demonstrated a positive proof of concept for lonigutamab in treating patients with TED. Lonigutamab provided rapid and meaningful clinical responses for proptosis and clinical activity score versus placebo. Further, those responses were observed within 3 weeks after first subcutaneous dose and were maintained through 12 weeks; six weeks after last dose and accompanied a well-tolerated safety profile. Lonigutamab demonstrates that it is a high potency anti-IGF-1R with a unique impact on the IGF-1R axis enabling the potential to optimize benefit-risk towards more complete resolution of disease. Clinically meaningful responses achieved at lower exposures relative to standard of care.

Third Cohort

[0429] Based on the interim successes seen in Cohorts 1-2, and to provide further safety, efficacy, and dose profile data, Cohort 3 was entered into the trial. The demographics of Cohort 3 are outlined in FIG. 28, and are similar to those of Cohorts 1-2. As shown, Cohort 3 will receive lonigutamab at 50 mg Q4W. FIG. 9B outlines the schedule of dosing and follow up for Cohort 3.

[0430] FIG. 27 outlines the rationale for the 50 mg Q4W dose regime. Cohort 3 was designed to test a "Cohort 1" like exposure, but continued for 12 weeks. This corroborates and confirms Cohort 1 results, while also providing results regarding a longer treatment duration. Cohort 3 was also designed to explore if a lower C_{min} impacts efficacy responses. Emerging data by the present inventors suggests that a low C_{min} may be suboptimal for an early response.

[0431] FIG. 29 provides proptosis responses through week 12 for Cohort 3. As shown, 63% of patients had a proptosis response (defined as a $\geq$ 2mm reduction in proptosis) at week 6 (mean change of -1.9), which dropped to 29% at week 12 (mean change of -1.4). FIG. 30 provides the proptosis mean change data through week 12.

[0432] FIG. 31 provides clinical activity scores (CAS) and changes from baseline at weeks 6 and 12 for Cohort 3. A $\geq$ 2-point reduction in CAS is considered a clinically meaningful improvement for patients. At week 6, 75% of patients achieved a $\geq$2-point CAS reduction (study eye). At week 12 71% of patients achieved the CAS reduction. Mean (SD) change in CAS from baseline for the study eye with lonigutamab was −2.5 at week 6 and −3.1 at week 12.

[0433] Fig. 33 provides diplopia responses observed in Cohort 3 at weeks 6 and 12 for Cohort 3. As shown, the responses are clinically meaningful. Fig. 33 shows the diplopia response through week 12 for patients of Cohort 3 with baseline diplopia >0.

[0434] Fig. 34 provides the results of GO-Quality of Life survey for Cohort 3 starting from before treatment through week 12. The original value and change from Baseline/Day 1 in the GO-QoL questionnaire overall and subscale scores are summarized descriptively by treatment group and visit. As shown, there was an improvement during the treatment period for those receiving lonigutamab, which remained elevated relative to the starting value through week 12.

[0435] Fig. 35 provides a summary of efficacy for Cohorts 1-3 in comparison to teprotumumab. Fig. 36 provides a summary of efficacy responses (proptosis responder rate and CAS responder rate) for Cohorts 1-3. As shown in Fig. 36, the Cohort 2 diplopia response was consistent from week 4 through week 12 (50%). For Cohort 3, the response was consistent from week 4 through week 8. These responses model mimic the PK modeling, which suggests a week 6 peak compared to weeks 4, 8, and 12 (trough). Fig. 37 summarizes the diplopia changes among Cohorts 1-3. As shown, the biggest improvement was seen in Cohort 3, both in terms of numbers of patients responding and the magnitude of the change. This change remained fairly stable through week 12.

[0436] Fig. 38 summarizes the safety data for Cohorts 1-3. As shown, for Cohort 3, there were no serious adverse events, and the safety profile appeared, if anything, improved over Cohorts 1-2. As shown in Fig. 39, one patient in Cohort 3 did report mild tinnitus. The patient was exposed to loud noises at work and was on escitalopram. The tinnitus was not associated with changes on the audiogram or treatment interruption. Audiology reports associated with Cohorts 1-3 is provided in Figs. 40A-40H.

Fourth Cohort

[0437] As discussed, the safety data for the Cohort 3 dose indicated a positive safety profile, in line with the doses of Cohorts 1-2. Further, the diplopia response for Cohort 3 appeared to improve upon those from Cohorts 1-2. However, while the peak proptosis responder rates for Cohort 3 met those of Cohort 2, they tailed off after week 6, as did the CAS responder rates. In contrast, these values remained stable or improved for patients of Cohort 2.

[0438] Consequently, based on the decision tree outlined in Fig. 27, a fourth cohort (Cohort 4) was enrolled in the trial.

[0439] Fig. 41 outlines does profile for Cohort 4, and the underlying rationale. As shown, Cohort 4 receives lonigutamab at 70 mg Q3W or QW4. Modeling suggests that a 70 mg Q3W does regime best maintains drug levels within an equivalent Cmax and Cmin (potency adjusted) as found in tepro, which approximates target-mediated drug disposition (TMDD) thresholds. The population

PK model estimated IGF1-R concentration of 1.5 ug/mL, which will allow the receptor to be fully saturated and reduce the risk of target mediated drug disposition (e.g., fast clearance). Maintains Drug Levels Within Equivalent (Potency Adjusted).

[0440] Relative to the patients of Cohorts 1-3, the patients of Cohort 4 show an improved efficacy profile due to the higher Q3W or Q4W dose.

Example 3 - A Phase 3, Randomized, Double-Masked, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lonigutamab in Subjects with Thyroid Eye Disease

[0441] This study evaluates the efficacy, safety, PK, and PD of lonigutamab in subjects with TED. The single ascending dose (SAD) study (in healthy subjects), multiple-dose study (in healthy subjects), and multiple-dose study (in subjects with TED), outlined in the Examples above, indicate that lonigutamab appears safe and well-tolerated, based on emerging data. The lonigutamab regimen in this study (100 mg loading dose + 50 mg Q2W) was selected based on available safety, PK, PD, and efficacy data from those studies for an optimal benefit-risk ratio.

[0442] In the studies outlined in the prior Examples, a total of 93 healthy subjects and subjects with TED were evaluated in the measured environs of 2 phase 1 clinical studies and a phase 1/2 clinical study of lonigutamab; 75 subjects received lonigutamab and 18 received placebo. Lonigutamab was studied both IV at a dosage range of 0.1 to 3.0 mg/kg and SC at 20 to 250 mg.

[0443] After reviewing all safety data available from these studies, there were no deaths, no serious adverse events and no unexpected trends or safety concerns identified in completed or then-ongoing studies of lonigutamab. The safety data support that lonigutamab is well-tolerated at all doses tested. Therefore, the overall benefit-risk assessment for subjects participating in the lonigutamab development program remained positive and supported the continued development of lonigutamab as a potential therapy for TED.

[0444] Prior to this study, the strategy for lonigutamab in human clinical studies has largely been to define the PK and PD profile and to evaluate dose response with respect to efficacy and safety, to optimize the benefit-risk ratio for patients with TED. Phase 1 and phase 2 clinical studies of lonigutamab aimed at a) identifying the lowest effective SC dose that maintains optimal receptor occupancy (RO) rates over the dosing interval, and b) defining an optimal exposure that sustains response in patients with TED with the goal of potentially reducing risks to support long-term use in the treatment of TED.

[0445] Lonigutamab was studied at an IV dosage range of 0.1 to 3.0 mg/kg and SC at 20 to 250 mg. Pre-specified adverse events of special interest (AESI) were observed for 4 (6.3%) subjects in a first study; no subjects in a second study; and 3 (50%) subjects in cohort 1, no subjects in cohort 2, and 1 (12.5%) subject in cohort 3 of study described above. Thus, lonigutamab appears to be safe and well tolerated.

[0446] The treatment effects of 4 different dosing regimens of lonigutamab on TED were evaluated in the phase 1/2 study. Subjects enrolled in cohort 1 received 2 SC doses of either lonigutamab 40 mg or placebo at an interval of Q3W. Subjects in cohort 2 received 12 doses of lonigutamab, consisting of a 50 mg SC loading dose followed by 11 additional doses of 25 mg SC once weekly. Subjects in cohort 3 received 3 doses of lonigutamab, consisting of 50 mg SC once every 4 weeks. Subjects in Cohort 4 received 70 or 100 mg SC once every 3 weeks (4 doses) or once every 4 weeks (3 doses). Data from cohorts 1, 2, and 3 demonstrate meaningful clinical responses for proptosis, clinical activity score (CAS), and diplopia in subjects with TED following treatment with SC lonigutamab, with preliminary data suggesting 50 mg Q4W may constitute a minimally effective dose. Modeling shows no PK difference in TED patients compared to healthy volunteers. Furthermore, RO results from cohorts 1 through 3 showed that all subjects reached maximal drug effect by the first post-treatment assessment (within 4 to 9 days), but suppression was not maintained through the dosing interval in cohort 3.

[0447] Based on emerging exposure of doses 40 mg and 50 mg and the respective preliminary clinical efficacy data from phase 1 and phase 1/2 clinical studies, which have demonstrated robust clinical improvement across TED manifestations, the optimal dose of lonigutamab for the phase 3 registrational studies is anticipated to be a 100 mg (2 × 50 mg) loading dose followed by 50 mg lonigutamab administered Q2W.

[0448] A population PK/PD model was developed based on lonigutamab concentrations and RO (percent of IGF-1R on the surface of CD4+ PBMCs or not bound by lonigutamab) (Fig. 42). The PK/PD model included data from Examples 1 and 2. Lonigutamab PK was adequately described by a 2-compartment model with target-mediated drug disposition (TMDD) while the observed PD effect was characterized by a direct response model. The PD model indicates that lonigutamab is a highly potent inhibitor of IGF-1R, with 90% of maximal effective concentration (EC90) of 0.1 μg/mL.

[0449] The 50 mg Q2W dose was selected as the phase 3 dose due to its ability to maintain a minimum plasma concentration (Cmin) greater than the TMDD threshold in > 80% of subjects during the dosing period (Fig. 42). The PK/PD model further predicts that RO is maximally achieved during the dosing period. A 100 mg loading dose enables faster time to steady state. The TMDD threshold for lonigutamab is estimated to be 1.5 μg/mL based on the population PK model. Thus, this study evaluates the efficacy, safety, and PK of lonigutamab 100 mg loading dose followed by 50 mg SC Q2W in subjects with TED.

Summary of Study Design

[0450] This is a multicenter, phase 3, randomized, double-masked, placebo-controlled study to evaluate the efficacy, safety, and pharmacokinetics (PK) of lonigutamab in subjects with thyroid eye disease (TED). The study will consist of 4 periods, which are outlined in Fig 43:

Screening period: day -28 to day -1

Treatment period 1: week 0/day 1 through to end of week 23

Treatment extension period: week 24 through to end of week 51

Follow-up period: week 52 through to week 62.

[0451] Screening and Randomization: Subjects undergo screening within 28 days before day 1. 175 adult subjects with TED (including at least 81 subjects with TED for ≤ 15 months and Clinical Activity Score (CAS) ≥ 3 at baseline) who meet all eligibility criteria are randomized 2:1 to receive double-masked investigational product lonigutamab for both treatment periods (52 weeks for the lonigutamab group, n ~ 117) or matching placebo during treatment period 1 and lonigutamab during the 28-week treatment extension period (placebo group, n ~ 58). For the purposes of this Example, the term study drug refers to both lonigutamab and placebo.

[0452] Randomization is stratified by TED for ≤ 15 months and CAS ≥ 3 at baseline (yes vs no) and by diplopia status at baseline (yes vs no). Enrollment of subjects without diplopia at baseline is capped at 25%. Enrollment is capped at 50% for subjects with the following audiometry baseline values for frequencies above 2000 Hz: 20 to 40 dB hearing level (HL) decrease for subjects < 45 years of age; and 20 to 55 dB HL decrease for subjects 45 years or older.

[0453] Treatment period 1: Subjects receive a one-time loading dose of 100 mg (2 × 50 mg) SC lonigutamab (or matching placebo) on day 1/week 0, followed by 50 mg SC injections of lonigutamab (or matching placebo) every 2 weeks (Q2W) until week 22 for a total of 12 doses.

[0454] Treatment extension period: At week 24, all subjects enter the treatment extension period and receive treatment with lonigutamab. Subjects who received lonigutamab during treatment period 1 receive 1 dose of lonigutamab 50 mg SC and 1 dose of placebo on week 24 to maintain the double-masked nature of the study. Subjects who received placebo during treatment period 1 receive a one-time loading dose of 100 mg SC lonigutamab (administered as 2 × 50 mg doses) at week 24. All subjects receive lonigutamab 50 mg SC Q2W from week 26 through to week 50 (last dose).

[0455] Follow-Up Period: The follow-up period includes an end-of-treatment (EOT)/early termination (ET) visit at week 52 and an end-of-study (EOS) visit at week 62 for safety and efficacy assessments.

[0456] Subjects randomized to the lonigutamab group who complete both treatment periods receive a total of 26 doses of lonigutamab, and subjects randomized to the placebo group who complete both treatment periods receive 14 doses of lonigutamab. The study will consist of a 28-day screening period, a 52-week treatment period (comprising treatment period 1 and the treatment extension period), and a 10-week follow-up period. The maximum study duration will be 66 weeks per subject.

[0457] Clinical measures of TED include an assessment of proptosis (exophthalmos), CAS, diplopia (Gorman scale and diplopia questionnaire), motility restriction, subject assessment of eye and orbital pain, Graves' Ophthalmopathy Quality of Life (GO-QoL), European Quality of Life-5 dimension scale (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP), magnetic resonance imaging (MRI)/computed tomography (CT) scans (participating sites and subjects only), and facial photographs (participating sites and subjects only).

[0458] Safety assessments include physical examination, vital signs and body measurements, ophthalmic safety examinations, electrocardiograms (ECG), audiology, clinical laboratory tests, and adverse event monitoring. Other study evaluations include PK, PD, immunogenicity, and exploratory biomarker assessments.

Estimands

[0459] ***Primary Estimand***: The components of the estimand to address the primary objective to demonstrate the superiority of lonigutamab compared to placebo as measured by the proptosis responder rate at week 24 are as follows:

[0460] *First primary objectives*:

[0461] Treatment: lonigutamab versus placebo. The primary treatment condition of interest is lonigutamab Q2W from week 0/day 1 to week 52. The reference treatment is placebo Q2W from week 0/day 1 to week 22, transitioning to lonigutamab Q2W from week 24 to week 52. Population of interest: subjects with TED who meet onset of TED for ≤ 15 months and CAS ≥ 3 at baseline criteria. Variable of interest: achievement of proptosis responder rate -at week 24. Summary measure: response rate, percentage of subjects with ≥ 2 mm reduction of proptosis (exophthalmometry) in the study eye from baseline (day 1) without deterioration (≥ 2 mm increase) of proptosis in the contralateral eye (responder/non-responder). Intercurrent event (ICE) handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, or protocol deviations.

[0462] *Second primary objective:*

[0463] Treatment: lonigutamab versus placebo. The primary treatment condition of interest is lonigutamab Q2W from week 0/day 1 to week 52. The reference treatment is placebo Q2W from week 0/day 1 to week 22, transitioning to lonigutamab Q2W from week 24 to week 52. Population of interest: all subjects who are randomized. Variable of interest: achievement of proptosis responder rate at week 24. Summary measure: response rate, percentage of subjects with ≥ 2 mm reduction of proptosis (exophthalmometry) in the study eye from baseline (day 1) without deterioration (≥ 2 mm increase) of proptosis in the contralateral eye (responder/nonresponder). Intercurrent event (ICE) handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, or protocol deviations.

[0464] ***Secondary Estimands***

[0465] For each secondary objective, the treatment component of the estimand is lonigutamab Q2W from week 0/day 1 to week 52 versus placebo Q2W from week 0/day 1 to week 22, transitioning to lonigutamab Q2W from week 24 to week 52; the population of interest component of the estimand is subjects with TED who meet all inclusion/exclusion criteria; and the ICE handling component of the estimand is the treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication, or protocol deviations. The variable of interest and summary measure components of the estimand to address each secondary objective are as follows.

[0466] *First secondary objective*:

[0467] Summary measure: mean change from baseline in proptosis measurement (in mm) in the study eye.

[0468] *Second secondary objective*:

[0469] Variable of interest: percentage of subjects achieving a ≥ 2-point reduction in the CAS at week 24. Summary measure: response rate, defined as achievement of a ≥ 2-point reduction in the CAS in the study eye(responder/non-responder). Population of interest: subjects with baseline CAS ≥ 3, using 7-point scale.

[0470] *Third secondary objective:*

[0471] Variable of interest: overall responder rate, percentage of patients achieving an overall response at week 24. Summary measure: overall responder rate, defined as achievement of a ≥ 2 point reduction in the CAS and a ≥ 2 mm reduction in proptosis (exophthalmometry) in the study eye without deterioration (≥ 2 mm increase) of proptosis in the contralateral eye. Population of interest: subjects with baseline CAS ≥ 3, using 7-point scale.

[0472] *Fourth secondary objective:*

[0473] Variable of interest: diplopia responder rate, percentage of subjects achieving a diplopia response at week 24. Summary measure: response rate, defined as achievement of diplopia score reduction of ≥ 1 grade based on Gorman scale (responder/non-responder). Population of interest: subjects with baseline diplopia (Gorman diplopia score) > 0.

[0474] *Fifth secondary objective:*

[0475] Variable of interest: CAS of 0 or 1, percentage of subjects achieving total CAS 0 or 1 at week 24. Summary measure: binary rate, defined as achievement of total CAS 0 or 1 in the study eye. Population of interest: subjects with baseline CAS ≥ 3, using 7-point scale

[0476] *Sixth secondary objective:*

[0477] Variable of interest: change in GO-QoL at week 24. Summary measure: mean change from baseline in GO-QoL questionnaire overall scores.

[0478] *Seventh secondary objective:*

[0479] Variable of interest: diplopia resolution rate, percentage of subjects achieving a diplopia resolution at week 24. Summary measure: diplopia resolution rate, defined as achievement of diplopia score of 0 based on Gorman scale (responder/non-responder). Population of interest: subjects with baseline diplopia (Gorman diplopia score) > 0.

[0480] As expected, and in line with the data obtained in Examples 1 and 2, the safety data for patients receiving 50 mg lonigutamab Q2W from week 0/day 1 to week 52 after a loading dose of 100 mg lonigutamab indicates a positive safety profile, highly therapeutic diplopia response, stable and high peak proptosis responder rates and CAS responder rates.

Incorporation by Reference

[0481] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, publicly accessible databases, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

[0482] Various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

Table 1 – Schedule of Assessments for Cohort 1

	Screening Period	**Treatment Period**		**Follow-up Period**			
Clinic Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOS**
Day (D)	**Screening D-28 to D-1**	**Baseline/Day 1 D1**	**D21**	**D43**	**D57**	**D85**	**D113**
Visit Window (± days)			**±2**	**±2**	**±2**	**±3**	**±3**
Informed consent	X						
Review inclusion/exclusion criteria	X	X					

Demographic data	X						
Medical and medication histories	X	X					
Review and monitoring of AEs[a]		X	X	X	X	X	X
Review SAEs and concomitant medications	X	X	X	X	X	X	X
Physical examination[b]	X	X	X	X	X	X	X
Ophthalmic examination[c]	X	X	X	X	X	X	X
Clinical Measures of TED[d]	X	X	X	X	X	X	
Height and Weight	X						X[e]
Vital signs (BP, HR, RR, and body temperature)[f]	X	X	X	X	X	X	X
12-lead ECG	X		X	X			X
Hematology	X	X	X	X	X	X	X
Biochemistry (includes glucose)	X	X	X	X	X	X	X
HbA1c	X	X	X	X	X	X	X
QuantiFERON®-TB Test[g]	X						
Fecal calprotectin[h]	X						
Thyroid (FT3, FT4, TSH, TSI; TPO)	X			X		X	X
Serology (HIV, HBV, HCV)	X						
Serum pregnancy test	X						
Urine pregnancy test[i]		X	X		X		X
FSH[j]	X						
Urinalysis	X	X	X	X	X	X	X
Serum PK		X	X	X	X	X	X
Serum ADA		X	X	X	X	X	X
Serum IGF-1		X	X	X	X	X	X
PBMC-RO		X	X	X			X
	Screening Period	**Treatment Period**		**Follow-up Period**			
Clinic Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOS**
Day (D)	**Screening D-28 to D-1**	**Baseline/Day 1 D1**	**D21**	**D43**	**D57**	**D85**	**D113**
Visit Window (± days)			**±2**	**±2**	**±2**	**±3**	**±3**
Audiometry test	X						

Facial Photo Assessment	X		X	X		X	
Randomization		X					
Study treatment administration		X	X				
Injection site evaluation[k]		X	X	X			X
GO-QoL Questionnaire		X	X	X		X	
Pregnancy Counseling	X	X	X		X	X	X

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BP=blood pressure; CAS=Clinical Activity Score; D=day; ECG=electrocardiogram; EOS=End-of-Study Visit; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GO-QoL=Graves' Ophthalmopathy Quality of Life; HbA1c=glycated hemoglobin A1c; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; IGF-1=insulin-like growth factor-1; PBMC-RO=peripheral blood mononuclear cells – receptor occupancy; PK=pharmacokinetics; RR=respiratory rate; TB=tuberculosis; TED=thyroid eye disease; TPO=thyroid peroxidase antibodies; TSH=thyroid stimulating hormone; TSI=thyroid-stimulating immunoglobulin; W=week; WOCBP=women of childbearing potential.

[a] The period of observation for collection of AEs extends from the time the subject is administered study drug until the EOS follow-up visit.

[b] Complete physical examination at Screening and on Day 113; symptom-based physical examination at all other visits.

[c] Includes visual acuity, slit lamp evaluation, marginal reflex distance, and intraocular pressure.

[d] Includes proptosis, diplopia, and CAS.

[e] Only the subject's weight will be assessed at the EOS Visit.

[f] Includes systolic and diastolic blood pressure, heart rate, and respiration rate while the subject is at rest, and body temperature. On dosing days, vital signs will be measured before study drug administration and 1 hour after study drug administration (±15 minutes).

[g] A QuantiFERON®-TB test is only required for subjects meeting the test criteria for subjects as listed in Exclusion Criteria #20. The test will be performed for subjects meeting criteria listed in Exclusion Criterion #20 unless documented results are available within 2 months preceding the first dose. Test may be done locally or with central laboratory.

[h] Only for subjects as outlined in Exclusion Criterion #2.

[i] For WOCBP, if a urine pregnancy test is positive, a confirmatory serum pregnancy test will be conducted.

[j] Postmenopausal status will be confirmed through testing of FSH levels (≥40 IU/mL) at Screening for amenorrheic female subjects.

[k] Injection site evaluation prior to and for 1 hour after study drug administration on Day 1 and Day 21. Soft tissue evaluation on Day 43 and 113.

Table 2 Additional Pharmacokinetic and Pharmacodynamic Sampling Schedule for Cohort 1

Day (D)	**D2**	**D3**	**D9**	**D15**	**D25**	**D29**	**D34**	**D39**
Visit Window (± days)	**±2 hours**	**±2 hours**	**±1**	**±2**	**±2**	**±2**	**±2**	**±2**
Serum PK	X	X	X	X	X	X	X	X
Serum PD			X	X				
PBMC–RO			X	X				

Abbreviation: D=Day; PBMC-RO=peripheral blood mononuclear cells – receptor occupancy; PD=pharmacodynamic; PK=pharmacokinetic.
Note: These samples may be collected via home health nurse.

TABLE 3 – Schedule of Assessments for Cohort 2

	Screening Period	Treatment Period																Follow-up Period		
Clinic Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/EOS**			
Week (W)	**Screening W-4 to W-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24**			
Day (D)	**Screening D-28 to D-1**	**Baseline/ Day 1 D1**	**D8**	**D15**	**D22**	**D29**	**D36**	**D43**	**D50**	**D57**	**D64**	**D71**	**D78**	**D85**	**D113**	**D141**	**D169**			
Visit Window (± days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**			
Informed consent	X																			
Review inclusion/exclusion criteria	X	X																		
Demographic data	X																			
Medical and medication histories	X	X																		
Review and monitoring of AEs[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Review SAEs and Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination[b]	X	X				X		X		X				X	X	X	X			

Ophthalmic examination[e]	X	X			X		X		X			X	X	X	X	X
Clinical Measures of TED[d]	X	X			X		X		X			X	X	X	X	X
GO-QoL Questionnaire		X			X		X		X			X	X			X
Height and Weight	X															X[e]
Vital signs (BP, HR, RR, and body temperature)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X															
Hematology	X	X			X			X					X	X	X	X
Biochemistry (includes glucose)	X	X			X			X					X	X	X	X
HbA1c	X	X			X			X					X	X	X	X
QuantiFERON®-TB Test[g]	X															
Fecal calprotectin[h]	X															
Thyroid (FT3, FT4, TSH, TSI; TPO)	X	X			X			X					X	X		X
Serology (HIV, HBV, HCV)	X															
Serum pregnancy test	X															
Urine pregnancy test[i]		X			X			X					X	X	X	X
FSH[j]	X															
Urinalysis	X	X			X			X					X	X	X	X
Serum PK		X	X	X		X	X		X				X	X	X	X
Serum ADA		X		X	X				X				X	X	X	X

Serum IGF-1		X	X	X		X		X		X			X	X	X	X
PBMC-RO		X	X	X		X		X		X			X	X	X	X
Audiometry test[k]	X							X					X		X	
Facial Photo Assessment	X							X					X			X
Pregnancy Counseling	X	X					X				X			X	X	X
Study treatment administration		X	X	X	X	X	X	X	X	X	X	X	X			
Clinical Site visits	X	X	X	X	X[l] (optional)	X	X[l] (optional)	X	X[l] (optional)	X	X[l] (optional)	X[l] (optional)	X[l] (optional)	X	X	X
Injection site evaluation[m]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BP=blood pressure; CAS=Clinical Activity Score; D=day; ECG=electrocardiogram; EOS=End-of-Study Visit; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GO-QoL=Graves' Ophthalmopathy Quality of Life; HbA1c=glycated hemoglobin A1c; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; IGF-1=insulin-like growth factor-1; PBMC-RO=peripheral blood mononuclear cells – receptor occupancy; PK=pharmacokinetics; RR=respiratory rate; TB=tuberculosis; TED=thyroid eye disease; TPO=thyroid peroxidase antibodies; TSH=thyroid stimulating hormone; TSI=thyroid-stimulating immunoglobulin; W=week; WOCBP=women of childbearing potential.

a. The period of observation for collection of AEs extends from the time the subject is administered study drug until the EOS follow-up visit.

b. Complete physical examination at Screening and on Day 169 (Cohort 2); symptom-based physical examination at all other visits.

c. Includes visual acuity, slit lamp evaluation, marginal reflex distance, and intraocular pressure.

d. Includes proptosis, diplopia, and CAS.

e. Only the subject's weight will be assessed at the EOS Visit.

f. Includes systolic and diastolic blood pressure, heart rate, and respiration rate while the subject is at rest, and body temperature. On dosing days, vital signs will be measured before study drug administration and 1 hour after study drug administration (+/-15 minutes). Vital sign measurements are not required on days of home health visits.

g. A QuantiFERON®-TB test is only required for subjects meeting the test criteria for subjects as listed in Exclusion Criteria #20. The test will be performed for subjects meeting criteria listed in Exclusion Criterion #20 unless documented results are available within 2 months preceding the first dose. Test may be done locally or with central laboratory.

h. Only for subjects as outlined in Exclusion Criterion #2.

i. For WOCBP, if a urine pregnancy test is positive, a confirmatory serum pregnancy test will be conducted.

j. Postmenopausal status will be confirmed through testing of FSH levels (•40 IU/mL) at Screening for amenorrheic female subjects.

k. Audiometry should also be performed as clinically indicated.

l. For Cohort 2, subjects may be given the option to have D22, D36, D50, D64, D71, and D78 visits at their home with a home health nurse, who will prepare and administer study drug.

m. Injection site evaluation prior to and for 1 hour after study drug administration on dosing days. Soft tissue evaluation on Day 85 and during Follow-up Period. (post-drug administration injection site evaluation not required on home dosing days)

Table 4 – Schedule of Assessments for Cohort 3

	Screening Period	Treatment Period							Follow-up Period		
Clinic Study Visit	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**14**	**15**	**16**	**17/EOS**
Week (W)	**Screening W4 to W-1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**
Day (D)	**Screening D-28 to D-1**	**Baseline/ Day 1 D1**	**D8**	**D15**	**D29**	**D43**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window (± days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±3**	**±3**
Informed consent	X										
Review inclusion/exclusion criteria	X	X									
Demographic data	X										
Medical and medication histories	X	X									
Review and monitoring of AEs[a]		X	X	X	X	X	X	X	X	X	X

Review SAEs and Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Physical examination[b]	X	X			X	X	X	X	X	X	X
Ophthalmic examination[c]	X	X			X	X	X	X	X	X	X
Clinical Measures of TED[d]	X	X			X	X	X	X	X	X	X
GO-QoL Questionnaire		X			X	X	X	X	X		X
Height and Weight	X										X[e]
Vital signs (BP, HR, RR, and body temperature)[f]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X										
Hematology	X	X			X		X	X	X	X	X
Biochemistry (includes glucose)	X	X			X		X	X	X	X	X
HbA1c	X	X			X		X	X	X	X	X
QuantiFERON®-TB Test[g]	X										
Fecal calprotectin[h]	X										
Thyroid (FT3, FT4, TSH, TSI; TPO)	X	X			X		X	X	X		X
Serology (HIV, HBV, HCV)	X										
Serum pregnancy test	X										
Urine pregnancy test[i]		X			X		X	X	X	X	X
FSH[j]	X										
Urinalysis	X	X			X		X	X	X	X	X
Serum PK		X	Xk	X[k]	X	X	X	X	X	X	X
Serum ADA		X		X[k]	X		X	X	X	X	X
Serum IGF-1		X	X[k]	X[k]	X	X	X	X	X	X	X

PBMC-RO		X	X[k]	X[k]	X	X	X	X	X	X	X	X
Audiometry test[l]	X						X		X		X	
Facial Photo Assessment	X						X		X			X
Pregnancy Counseling	X	X			X			X	X	X	X	X
Study treatment administration		X			X			X				
Clinical Site visits	X	X			X	X	X	X	X	X	X	X
Injection site evaluation[m]		X	X	X	X	X	X	X	X	X		X

Abbreviations: ADA=antidrug antibodies; AE=adverse event; BP=blood pressure; CAS=Clinical Activity Score; D=day; ECG=electrocardiogram; EOS=End-of-Study Visit; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GO-QoL=Graves' Ophthalmopathy Quality of Life; HbA1c=glycated hemoglobin A1c; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=heart rate; IGF-1=insulin-like growth factor-1; PBMC-RO=peripheral blood mononuclear cells – receptor occupancy; PK=pharmacokinetics; RR=respiratory rate; TB=tuberculosis; TED=thyroid eye disease; TPO=thyroid peroxidase antibodies; TSH=thyroid stimulating hormone; TSI=thyroid-stimulating immunoglobulin; W=week; WOCBP=women of childbearing potential.

a. The period of observation for collection of AEs extends from the time the subject is administered study drug until the EOS follow-up visit.
b. Complete physical examination at Screening and on Day 169 (Cohort 3); symptom-based physical examination at all other visits.
c. Includes visual acuity, slit lamp evaluation, marginal reflex distance, and intraocular pressure.
d. Includes proptosis, diplopia, and CAS.
e. Only the subject's weight will be assessed at the EOS Visit.
f. Includes systolic and diastolic blood pressure, heart rate, and respiration rate while the subject is at rest, and body temperature. On dosing days, vital signs will be measured before study drug administration and 1 hour after study drug administration (+/-15 minutes). Vital sign measurements are not required on days of home health visits.
g. A QuantiFERON®-TB test is only required for subjects meeting the test criteria for subjects as listed in Exclusion Criteria #20. The test will be performed for subjects meeting criteria listed in Exclusion Criterion #20 unless documented results are available within 2 months preceding the first dose. Test may be done locally or with central laboratory.
h. Only for subjects as outlined in Exclusion Criterion #2.
i. For WOCBP, if a urine pregnancy test is positive, a confirmatory serum pregnancy test will be conducted.
j. Postmenopausal status will be confirmed through testing of FSH levels (≥40 IU/mL) at Screening for amenorrheic female subjects.
k. These samples may be collected via home health nurse for Cohort 3 subjects.

l. Injection site evaluation prior to and for 1 hour after study drug administration on dosing days. Soft tissue evaluation on Day 85 and during Follow-up Period.

m. Audiometry should also be performed as clinically indicated.

Table 5 Additional Pharmacokinetic and Pharmacodynamic Sampling Schedule for Cohort 2 and Cohort 3

Day (D)	D4	D32	D60	D81	D92	D99	D106
Visit Window (± days)	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	**±2**
Serum PK	X	X	X	X	X	X	X
Serum PD	X	X	X	X	X	X	X
PBMC-RO	X	X	X	X	X	X	X

PD=pharmacodynamics; PK=pharmacokinetics; PBMC-RO=peripheral blood mononuclear cells-receptor occupancy. These samples may be collected via home health nurse.

Table 6 - Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ≥5 × ULN
ALT or AST Increase	ALT or AST ≥3 × ULN persists for ≥4 weeks
Bilirubin[1,2]	ALT or AST ≥3 × ULN **and** total bilirubin ≥2 × ULN (>35% direct bilirubin)
International Normalized Ratio (INR)[2]	ALT or AST ≥3 × ULN **and** INR >1.5
Cannot Monitor	ALT or AST ≥3 × ULN and cannot be monitored twice weekly for 4 weeks
Symptomatic[3]	ALT or AST ≥3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions, Monitoring, and Follow-up Assessments	

Actions • **Immediately** discontinue study drug. Report the event to the sponsor/designee **within 24 hours**. • Complete a serious adverse event (SAE) eCRF if the event met the criteria for an SAE.[2] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the subject until liver chemistry test abnormalities resolve, stabilize, or return to baseline. **MONITORING:** **If ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and • INR) and perform liver event follow-up assessments within **24 hours**. • Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A hepatology consultation is recommended. **If ALT or AST ≥ 3 × ULN AND total bilirubin × ULN and INR ≥1.5:** • Repeat liver chemistry tests (include ALT, • AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**. • Monitor subjects twice weekly until liver chemistry abnormalities resolve,	**Follow-up Assessments** • Viral hepatitis serology.[3] • Obtain blood samples for pharmacokinetic (PK) analysis after the most recent dose.[4] • Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma glutamyl transferase, glutamate dehydrogenase, and serum albumin. • Fractionate bilirubin if total bilirubin ≥2 × ULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake form. • If ALT or AST ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5 obtain the following in addition to the assessments listed above: • Antinuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week.

stabilize, or return to baseline, or the study drug has been discontinued; then decrease monitoring to once weekly or less. • **Do not restart/rechallenge** subject with study drug unless allowed per-protocol and sponsor approval is granted.	• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease. • Liver biopsy may be considered and discussed with local specialist if available, for instance: • In subjects when serology raises the possibility of autoimmune hepatitis. • In subjects when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study drug. • In subjects with acute or chronic atypical presentation. • If liver biopsy conducted provides biopsy information.

Abbreviation: ALT = alanine transaminase; AST = aspartate transaminase; eCRF = electronic case report form; ULN = upper limit of normal.

1 Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

2 All events of ALT or AST ≥3 × ULN **and** total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT or AST ≥3 × ULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value does not apply to subjects receiving anticoagulants.

3 New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

4 Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug prior to the blood sample draw on the eCRF. If the date/time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Laboratory Manual.

Table 7 – Laboratory Assessments		
Hematology/Coagulation	**Serum Chemistry**	**Urine Analysis (Dipstick)**
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count WBC count with differential (incl. ANC, lymphocytes, monocytes eosinophils, basophils) INR	Albumin ALT ALP AST BUN or urea Carbon dioxide Creatinine Electrolytes (sodium, potassium, chloride, calcium) Glucose (non-fasting) Total bilirubin HbA1c	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urine β-HCG (WOCBP) Urobilinogen
Other Assessments	**Thyroid panel**	**Serology**
PK PD ADA PBMC	FT3 FT4 TSH TSI TPO	HIV HBV HCV
Pregnancy test: A serum pregnancy test is performed on all women of childbearing potential at Screening. A urine pregnancy test is performed at the timepoints specified in Schedules of Assessments (Table 1, Table 3, and Table 4).		
QuantiFERON®-TB test: Performed only for subjects meeting test criteria listed in Exclusion Criterion #20 unless documented results are available within 2 months preceding dosing.		
FSH: Postmenopausal status is confirmed through testing of FSH levels (•40 IU/mL) at Screening for amenorrheic female subjects.		
Fecal calprotectin test: as needed per exclusion criteria #2.		
INR test: as needed per liver chemistry stopping criteria assessment.		
Abbreviations: ADA = antidrug antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HCG = human chorionic gonadotropin; BUN = blood urea nitrogen; FT3 = free triiodothyronine; FT4 = free thyroxine; FSH = follicle-stimulating hormone; Hb = hemoglobin; HbA1c = glycated hemoglobin A1c; HBV = hepatitis B virus; Hct = hematocrit; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PD = pharmacodynamic; PK = pharmacokinetic; PBMC = peripheral blood mononuclear cells; RBC = red blood cell; TB = tuberculosis; TPO =		

thyroid peroxidase antibodies; TSH = thyroid stimulating hormone; TSI = thyroid-stimulating immunoglobulin; WBC = white blood cell; WOCBP = women of childbearing potential.

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CLAIMS

1. A method for treating thyroid eye disease (TED) in a subject, said method comprising administering a pharmaceutical composition comprising lonigutamab to a patient having TED.

2. The method of claim 1, wherein said pharmaceutical composition comprises between 10 mg and 250 mg of lonigutamab.

3. The method of any one of claims 1-2, wherein the pharmaceutical composition comprises at least 20 mg/ml, at least 25 mg/ml, at least 30 mg/ml, at least 40 mg/ml, at least 50 mg/ml, at least 60 mg/ml, at least 75 mg/ml, at least 100 mg/ml, at least 125 mg/ml, at least 150 mg/ml, at least 175 mg/ml, at least 200 mg/ml, or at least 250 mg/ml.

4. The method of any one of claims 1-3, wherein the pharmaceutical composition comprises from 25 mg/ml to 250 mg/ml, from 30 mg/ml to 200 mg/ml, or from 40 mg/ml to 100 mg/ml of lonigutamab.

5. The method of any one of claims 1-4, wherein the pharmaceutical composition comprises about 25 mg/ml to about 100 mg/ml of lonigutamab.

6. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once weekly.

7. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every two weeks.

8. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every three weeks.

9. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every four (4) weeks.

10. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every five (5) weeks, six (6) weeks, or seven (7) weeks.

11. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every eight (8) weeks.

12. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every nine (9) weeks, ten (10) weeks, or eleven (11) weeks.

13. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered once every twelve (12) weeks.

14. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered at day 1 and day 14.

15. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered at day 1 and day 21.

16. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered at day 1 and day 28.

17. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered to patient once every two weeks, and wherein the pharmaceutical composition comprises about 40 to about 80 mg of lonigutamab.

18. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered to patient once every three weeks, and wherein the pharmaceutical composition comprises about 40 to about 80 mg of lonigutamab.

19. The method of any one of claims 1-5, wherein the pharmaceutical composition is administered to the patient once every four weeks, and wherein the pharmaceutical composition comprises about 40 to about 80 mg of lonigutamab.

20. The method of any one of claims 1-19, wherein the pharmaceutical composition is administered to the patient in a first loading dose on a first day of treatment.

21. The method of claim 20, wherein the loading dose comprises about 50 mg to about 150 mg lonigutamab.

22. The method of claim 21, wherein after the loading dose comprises about 80 mg to about 120 mg lonigutamab, and after said loading dose the patient receives a dose of the pharmaceutical composition once every two weeks, wherein the dose once every two weeks comprises about 40 mg to about 60 mg of lonigutamab.

23. The method of claim 22, wherein after the loading dose comprises about 100 mg lonigutamab, and after said loading dose the patient receives a dose of the pharmaceutical composition once every two weeks, wherein the dose once every two weeks comprises about 50 mg of lonigutamab.

24. The method of any one of claims 1-23, wherein the pharmaceutical composition comprises:

from 20 to 30 mM L-histidine;

from 0.01% to 0.03% polysorbate 80;

from 4% (w/v) to 6% (w/v) D-sorbitol; and,

wherein the pharmaceutical composition is at a pH of 5.5-6.5.

25. The method of claim 24, wherein the pharmaceutical composition comprises: (i) 50 mg/ml lonigutamab, (ii) 25 mM L-histidine, (iii) 5% (w/v) sorbitol, and (iv) 0.02% polysorbate 80 at pH 6.0.

26. The method of claim 23, wherein the pharmaceutical composition comprises: (i) 50 mg/ml lonigutamab, (ii) 25 mM L-histidine, (iii) 5% (w/v) sorbitol, and (iv) 0.02% polysorbate 80 at pH 6.0, and wherein the same composition is provided for both the loading dose and the 50 mg doses.

27. The method of any one of claims 24-26, wherein the pharmaceutical composition:

comprises about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, about 25 mM, about 26 mM, about 27 mM, about 28 mM, about 29 mM, or about 30 mM histidine;

comprises about 4%, 5%, or 6% D-sorbitol; and/or

is at a pH of about 5.5, about 5.6, about 5.7, about 5.8, about 5.9, about 6.0, about 6.1, about 6.2, about 6.3, about 6.4, or about 6.5.

28. The method of any one of claims 1-27, wherein the osmolality of the pharmaceutical composition is within physiological osmolality range of 250-400mOsm/kg.

29. The method of any one of claims 1-28, wherein the pharmaceutical composition has a viscosity of no more than 30 cP at 21°C.

30. The method of any one of claims 1-29, wherein the pharmaceutical composition has a viscosity of no more than 15 cP at 21°C.

31. The method of any one of claims 1-28, wherein the viscosity of the pharmaceutical composition is about 10 cP, about 11 cP, about 12 cP, about 13 cP, about 14 cP, about 15 cP, about 16 cP, about 17 cP, about 18 cP, about 19 cP, about 20 cP, about 21 cP, about 22 cP, about 23 cP, about 24 cP, about 25 cP, about 26 cP, about 27 cP, about 28 cP, about 29 cP, or about 30 cP at 21°C.

32. The method of any one of claims 1-31, wherein the pharmaceutical composition is stable for at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 11 weeks, at least 12 weeks, at least 13 weeks, at least 14 weeks, at least 15 weeks, or at least 16 weeks.

33. The method of any one of claims 1-32, wherein the pharmaceutical composition is stable at a temperature of from -70°C to 40°C.

34. The method of any one of claims 1-33, wherein the pharmaceutical composition is administered subcutaneously.

35. The method of any one of claims 1-33, wherein the pharmaceutical composition is administered intramuscularly.

36. The method of any one of claims 1-35, wherein the pharmaceutical composition is administered in a delivery volume of no more than 2 ml.

38. The method of any one of claims 34-36, wherein the pharmaceutical composition is administered via a needle of a size of no bigger than 27G.

39. The method of any one of claims 34-36, wherein the pharmaceutical composition is administered via a needle of a size of no bigger than 26G.

40. The method of any one of claims 34-36, wherein the pharmaceutical composition is administered via a needle of a size of no bigger than 25G.

41. The method of any one of claims 34-36, wherein the pharmaceutical composition is administered via a needle of a size of no bigger than 24G.

42. The method of any one of claims 26-41, wherein the pharmaceutical composition is administered with an injection force of no more than 12N.

43. The method of claim 42, wherein the pharmaceutical composition is administered with an injection force of about 4N, about 5N, about 6N, about 7N, about 8N, about 9N, about 10N, about 11N, or about 12N.

44. The method of any one of claims 1-43, wherein the method reduces the severity of the thyroid eye disease (TED) in the subject.

44. The method of any one of claims 1-44, wherein the method reduces proptosis in the subject.

45. The method of claim 44, wherein proptosis is reduced by at least 2 mm.

46. The method of claim 44, wherein proptosis is reduced by at least 3 mm.

47. The method of claim 44, wherein proptosis is reduced by at least 4 mm.

48. The method of any one of claims 1-47, wherein the method reduces Clinical Activity Score (CAS) of thyroid eye disease (TED).

49. The method of claim 48, wherein the clinical activity score (CAS) is reduced by at least 2 points.

50. The method of claim 48, wherein the clinical activity score (CAS) is reduced to one (1).

51. The method of claim 48, wherein the clinical activity score (CAS) of the subject is reduced to zero (0).

52. The method of any one of claims 1-51, wherein the method improves the quality of life in the subject.

53. The method of claim 52, wherein the quality of life is measured by the Graves' Ophthalmopathy Quality of Life (GO-QoL) assessment.

54. The method of claim 52, wherein the quality of life is measured by the Visual Functioning or Appearance subscale thereof.

55. The method of claim 52, wherein the quality of life is measured by the European Group on Graves' orbitopathy (EUGOGO) guidelines.

56. The method of any one of claims 1-55, wherein the method reduces the severity of diplopia.

57. The method of claim 56, wherein the diplopia is constant diplopia.

58. The method of claim 56, wherein the diplopia is inconstant diplopia.

59. The method of claim 56, wherein the diplopia is intermittent diplopia.

60. An injector comprising the pharmaceutical composition of any one of claims 1-27.

61. The injector of claim 60, wherein the injector comprises a delivery volume of no more than 2 ml.

62. The injector of claim 60 or 61, wherein the injector comprises a needle of a size of no bigger than 24G.

63. The injector of claim 60 or 61, wherein the injector comprises a needle of a size of no bigger than 24G.

64. The injector of claim 60 or 61, wherein the injector comprises a needle of a size of no bigger than 25G.

65. The injector of claim 60 or 61, wherein the injector comprises a needle of a size of no bigger than 26G.

66. The injector of claim 60 or 61, wherein the injector comprises a needle of a size of no bigger than 27G.

67. The injector of any one of claims 60-66, wherein the injector is an automatic reusable fix dose Pen.

68. The injector of any one of claims 60-66, wherein the injector is an automatic reusable variable dose Pen.

69. The injector of any one of claims 60-66, wherein the injector is an automatic disposable fix dose autoinjector.

70. A method of treating thyroid eye disease (TED) comprising administering the pharmaceutical composition using the injector of any one of claims 60-69.

71. The method of claim 70, wherein the pharmaceutical composition is administered subcutaneously.

72. The method of claim 70, wherein the pharmaceutical composition is administered intramuscularly.

73. The method of any one of claims 70-72, wherein the pharmaceutical composition is administered with an injection force of no more than 12N.

74. The method of claim 73, wherein the pharmaceutical composition is administered with an injection force of about 4N, about 5N, about 6N, about 7N, about 8N, about 9N, about 10N, about 11N, or about 12N.

75. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about .1 μg/mL or higher.

76. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 1 μg/mL or higher.

77. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 2 μg/mL or higher.

78. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 3 μg/mL or higher.

79. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 3.5 μg/mL or higher.

80. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 4.0 μg/mL or higher.

81. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 4.5 μg/mL or higher.

82. The method of any one of claims 1-74, wherein the administration of a therapeutically effective dose of lonigutamab results in serum concentration of about 5 μg/mL or higher.