# METHODS FOR TREATING PRIMARY SJOGREN'S SYNDROME USING FCRN ANTAGONISTS

## CROSS REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of and priority to US Provisional Patent Application No. 63/569,943, filed March 26, 2024, the entire contents of which are hereby incorporated by reference in its entirety.

## FIELD

**[0002]** The present disclosure relates to methods of treating primary Sjögren's syndrome (pSS) and mitigating symptoms of pSS using efgartigimod and variations thereof.

## BACKGROUND

**[0003]** pSS is a chronic, progressive autoimmune disease of unclear etiology, typically presented as an exocrinopathy. Along with symptoms of extensive dryness, manifestations include profound fatigue, chronic pain, extraglandular organ system involvement, and increased risk of lymphomas. A hallmark of pSS is B cell hyperactivity, causing a vicious cycle of immune activation through cytokine production, antigen presentation, and autoantibody secretion, potentially causing tissue damage. Currently, no immunomodulatory treatment is available for pSS.

**[0004]** Currently, the underlying pathophysiology and effective treatments are unknown for pSS. Pharmacologic therapy mainly focuses on symptoms, targeting reducing discomfort associated with dry eyes and mouth and/or stimulation of tear and saliva production.

**[0005]** Accordingly, there is a need in the art for improved pSS treatment options that yield reliable efficacy signals for pSS symptoms.

**[0006]** Therapeutic antagonism of FcRn, a major histocompatibility complex class I-like molecule that is involved in the recycling of immunoglobulin G (IgG) and is thus responsible for the long half-life of IgG, has been explored as a strategy to treat IgG-mediated autoimmune diseases such as generalized myasthenia gravis (gMG), immune thrombocytopenia (ITP), and pemphigus (pemphigus vulgaris (PV) and pemphigus foliaceus (PF)). The remarkable clinical efficacy of FcRn antagonism appears to be directly linked to early removal of pathogenic IgG

autoantibodies from circulation. Unfortunately for patients, simply removing pathogenic IgG autoantibodies does not necessarily equate to meeting clinical endpoints or trial results, again highlighting the unpredictability of clinical trials. Efgartigimod has shown clinical success for gMG but saw trials fail to meet endpoints for use in treatment of PV and ITP using a subcutaneous formulation.

**[0007]** Pathogenic autoantibodies and immune complexes are involved in the development and/or progression of pSS. By reducing pathogenic autoantibodies and immune complexes, FcRn antagonists may provide a safer, more effective treatment option for patients with pSS. The clinical trial data shown in this disclosure establish support for efgartigimod as an effective treatment for pSS.

## SUMMARY

**[0008]** The instant disclosure is broadly directed to methods for treating pSS and related symptoms with FcRn antagonists.

**[0009]** The instant disclosure provides a method of treating pSS in a subject in need thereof, the method comprising administering to the subject an effective amount of a human neonatal Fc receptor (FcRn) antagonist and achieving a clinically established result. In some embodiments, the FcRn antagonist comprises or consists of a variant Fc region or FcRn binding fragment thereof. In some embodiments, the variant Fc region or FcRn binding fragment thereof binds to FcRn with a higher affinity at pH 6.0 as compared to a corresponding wild-type Fc region. In some embodiments the variant Fc region or FcRn binding fragment thereof binds to FcRn with a higher affinity at pH 7.4 as compared to a corresponding wild-type Fc region.

**[0010]** In some embodiments, the variant Fc region comprises or consists of a first Fc domain and a second Fc domain which form a homodimer or heterodimer. In some embodiments, the first Fc domain and/or the second Fc domain comprise amino acids Y, T, E, K, and F at EU positions 252, 254, 256, 433, and 434, respectively. In some embodiments, the first Fc domain and/or the second Fc domain comprise amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436, respectively.

**[0011]** In some embodiments, the first Fc domain and/or the second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4. In some embodiments, the first Fc domain and the

second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4.

**[0012]** In some embodiments, the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 1. In some embodiments, the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 2. In some embodiments, the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 3. In some embodiments, the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 4.

**[0013]** In some embodiments, the FcRn antagonist is a population of FcRn antagonist molecules, wherein each FcRn antagonist molecule in the population consists of a dimer of a first Fc domain and a second Fc domain, and wherein the population comprises:

(a) a first subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the first subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3; and

(b) at least one of:

(i) a second subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the second subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 12, respectively;

(ii) a third subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the third subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 9, respectively;

(iii) a fourth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the fourth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3, and wherein two asparagine residues in each FcRn antagonist molecule in the fourth subpopulation are deaminated;

(iv) a fifth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the fifth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 9, respectively,

and wherein one asparagine residue in each FcRn antagonist molecule in the fifth subpopulation is deaminated;

(v) a sixth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the sixth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively;

(vi) a seventh subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the seventh subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the seventh subpopulation is oxidized;

(vii) an eighth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the eighth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 2;

(viii) a ninth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the ninth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the ninth subpopulation is oxidized;

(ix) a tenth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the tenth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3, and wherein two amino acid residues, independently selected from a methionine residue and a tryptophan residue, in each FcRn antagonist molecule in the tenth subpopulation is oxidized; and

(x) an eleventh subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the eleventh subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 6, respectively.

**[0014]** In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[0015]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks. In some embodiments, the FcRn antagonist is administered intravenously at a dose of from 2 mg/kg to 200 mg/kg once weekly or once every two weeks. In

some embodiments, the FcRn antagonist is administered intravenously at a dose of 3 mg/kg to 60 mg/kg once weekly or once every two weeks. In some embodiments, the FcRn antagonist is administered intravenously at a dose of 10 mg/kg to 30 mg/kg once weekly or once every two weeks. In some embodiments, the FcRn antagonist is administered intravenously at a dose of 10 mg/kg once weekly or once every two weeks. In some embodiments, the FcRn antagonist is administered intravenously at a dose of 10 mg/kg once weekly.

**[0016]** In some embodiments, the FcRn antagonist is administered for 24 weeks or less. In some embodiments, the FcRn antagonist is administered for 24 weeks.

**[0017]** In some embodiments, the method further comprises administering to the subject an effective amount of one or more of a corticosteroid, a disease-modifying anti-rheumatic drug (DMARD), a non-steroidal anti-inflammatory agent, or a non-steroidal antirheumatic agent. In some embodiments, the corticosteroid is an oral corticosteroid administered to the subject at a dose of ≤10 mg/day. In some embodiments, the corticosteroid is a topical corticosteroid. In some embodiments, the DMARD is selected from the group consisting of hydroxychloroquine, chloroquine phosphate, methotrexate, azathioprine, and mycophenolate mofetil.

**[0018]** In some embodiments, the subject met the ACR-EULAR classification ≤7 years before administration of the FcRn antagonist.

**[0019]** In some embodiments, the subject has at least a moderate level of systemic disease activity before administration of the FcRn antagonist. In some embodiments, the subject has a EULAR Sjögren's syndrome disease activity index (ESSDAI) score of ≥5 before administration of the FcRn antagonist.

**[0020]** In some embodiments, the subject has a detectable serum level of a pSS-related autoantibody before administration of the FcRn antagonist. In some embodiments, the subject has a detectable serum level of an anti-Ro/SS-A antibody and/or an anti-La/SS-B antibody before administration of the FcRn antagonist.

**[0021]** In some embodiments, the subject has an unstimulated whole salivary flow (UWSF) rate >0 and/or a stimulated whole salivary flow (SWSF) rate >0.10 before administration of the FcRn antagonist.

**[0022]** In some embodiments, the subject shows three or more clinically established results following administration of the FcRn antagonist, wherein the clinically established results are selected from the group consisting of: a) a clinESSDAI score of <5 points; b) a decrease in ESSPRI score of ≥1 point or ≥15%, compared to a baseline value; c) an increase in tear gland function; d)

an increase in salivary gland function; and e) a decrease in serum RF of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value. In some embodiments, the responses are measured 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the responses are measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

**[0023]** In some embodiments, the subject shows a) a clinESSDAI score of <5 points; b) an increase in tear gland function; c) an increase in salivary gland function; and d) a decrease in serum RF of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value; following administration of the FcRn antagonist. In some embodiments, the responses are measured 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the responses are measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

**[0024]** In some embodiments, the increase in tear gland function is measured by Schirmer's test and/or ocular staining score (OSS), wherein if the subject shows a baseline value of ≤5 mm as measured by Schirmer's test, a response is defined as an increase of at least 5 mm from the baseline value; or if the subject shows a baseline value of ≥3 points as measured by OSS, a response is defined as a decrease of at least 2 points from the baseline value; or if the subject shows a baseline value of > 5 mm as measured by Schirmer's test and shows a baseline value of < 3 points as measured by OSS, a response is defined as no change that results in an abnormal OSS or Schirmer's score. In some embodiments, the responses are measured 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the responses are measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

**[0025]** In some embodiments, the increase in salivary gland function is measured by UWSF and/or salivary gland ultrasonography (SGUS), wherein a response is defined as an increase in UWSF of at least 25%, compared to a baseline value if the baseline value is > 0 mL/min, or any increase in UWSF if the baseline value is 0 mL/min; or a decrease in Hocevar score as measured by SGUS of at least 25%, compared to a baseline value. In some embodiments, the responses are measured 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the responses are measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

**[0026]** In some embodiments, the subject shows a decrease in ESSDAI score and/or clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value.

In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks. In some embodiments, the subject shows a decrease of at least 5 points in the ESSDAI score and/or the clinESSDAI score, following administration of the FcRn antagonist. In some embodiments, the subject has an ESSDAI score of <5 and/or a clinESSDAI score of <5, following administration of the FcRn antagonist.

**[0027]** In some embodiments, the subject shows an increase in Sjögren's Tool for Assessing Response (STAR) score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the STAR score is measured 24 weeks following administration of the FcRn antagonist. In some embodiments, the STAR score is measured following administration of the FcRn antagonist once weekly for 24 weeks. In some embodiments, the subject has a STAR score of ≥5 following administration of the FcRn antagonist.

**[0028]** In some embodiments, the subject shows a change in SWSF rate, UWSF rate, Hocevar score, Schirmer's test score, and/or OSS, following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured at 16 weeks or 24 weeks following administration of the FcRn antagonist. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

**[0029]** In some embodiments, the subject shows a reduction in a serum level of total IgG, RF, an autoantibody, or an immune complex following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the serum level of total IgG, RF, an autoantibody, or an immune complex is measured 4 weeks, 16 weeks, or 24 weeks following administration of the FcRn antagonist. In some embodiments, the serum level of total IgG, RF, an autoantibody, or an immune complex is measured following administration of the FcRn antagonist for 4 weeks, 16 weeks, or 24 weeks.

**[0030]** In some embodiments, the subject shows a reduction in a serum level of an autoantibody following administration of the FcRn antagonist. In some embodiments, the autoantibody is an anti-Ro52/SS-A antibody, an anti-Ro60/SS-A, or an anti-La/SS-B antibody.

**[0031]** In some embodiments, the subject shows a reduction in an immune complex following administration of the FcRn antagonist. In some embodiments, the immune complex is a C1q immune complex.

**[0032]** In some embodiments, the subject has a CRESS response of at least 45% when treated with efgartigimod when tested at 24 weeks following initial treatment with efgartigimod.

**[0033]** The instant disclosure also provides an FcRn antagonist for use in the treatment of pSS, wherein the treatment is performed according to the methods described above and herein, and wherein the treatment induces a CRESS response of at least 45% in subjects.

**[0034]** The instant disclosure also provides an FcRn antagonist for use in the manufacture of a medicament for the treatment of pSS, wherein the treatment is performed according to the methods described above and herein.

**[0035]** The instant disclosure also provides use of an FcRn antagonist for the treatment of pSS according to the methods described above and herein.

**[0036]** The instant disclosure also provides use of an FcRn antagonist for the manufacture of a medicament for treatment of pSS, wherein the treatment is performed according to the methods described above and herein.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0037]** **FIGs. 1A-1C** are graphs showing tear gland function as measured by Schirmer's Test from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0038]** **FIGs. 2A-2C** are graphs showing tear gland function as measured by ocular staining score (OSS) from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0039]** **FIGs. 3A-3C** are graphs showing salivary gland function as measured by unstimulated whole salivary flow (UWSF) rate from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0040]** **FIG. 4** is a graph showing salivary gland function as measured by salivary gland ultrasonography (SGUS; Hocevar score) from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0041]** **FIGs. 5A-5B** are graphs showing serum RF levels from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0042]** **FIGs. 6A-6D** are graphs showing serum autoantibody levels from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS. **FIG. 6A** shows serum anti-Ro52/SS-A levels, **FIG. 6B** shows median change (±IQR) from baseline in serum IgG and anti-Ro52/SS-A levels, **FIG. 6C** shows serum anti-Ro60/SS-A levels, and **FIG. 6D** shows serum anti-La/SS-B levels.

**[0043]** **FIG. 7** is a graph showing mean change (±SE) from baseline in C1q immune complex levels from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

**[0044]** **FIG. 8** is a graph showing Patient Global Assessment (PGA) scores from participants in a Phase 2 study investigating the efficacy and safety of efgartigimod for treatment of pSS.

## DETAILED DESCRIPTION

**[0045]** The present disclosure provides engineered FcRn antagonists and methods for their use in treating primary Sjögren's syndrome (pSS). Advantageously, the methods disclosed herein permit long-term reduction of pSS symptoms, reduction and/or prevention of glandular tissue destruction, and improvement in disease-related quality of life.

### Definitions

**[0046]** As used herein, the term "FcRn" refers to a neonatal Fc receptor. Exemplary FcRn molecules include human FcRn encoded by the FCGRT gene as set forth in RefSeq NM 004107. The amino acid sequence of the corresponding protein is set forth in RefSeq NP_004098.

**[0047]** As used herein, the term "FcRn antagonist" refers to any agent that binds specifically to FcRn and inhibits the binding of immunoglobulin to FcRn (*e.g.*, human FcRn).

**[0048]** As used herein, the term "Fc domain" refers to the portion of a single immunoglobulin heavy chain beginning in the hinge region and ending at the C-terminus of an antibody. Accordingly, a complete Fc domain comprises at least a portion of a hinge (*e.g.*, upper, middle, and/or lower hinge region) domain, a CH2 domain, and a CH3 domain. In some embodiments, the term "Fc domain" refers to the portion of a single immunoglobulin heavy chain

comprising both the CH2 and CH3 domains of an antibody. In some embodiments, the Fc domain comprises at least a portion of a hinge (*e.g.*, upper, middle, and/or lower hinge region) region, a CH2 domain, and a CH3 domain. In some embodiments, the Fc domain does not include the hinge region.

**[0049]** As used herein, the term "hinge region" refers to the portion of a heavy chain molecule that joins the CH1 domain to the CH2 domain. In some embodiments, the hinge region is at most 70 amino acid residues in length. In some embodiments, this hinge region comprises approximately 11-17 amino acid residues and is flexible, thus allowing the two N-terminal antigen binding regions to move independently. In some embodiments, the hinge region is 12 amino acid residues in length. In some embodiments, the hinge region is 15 amino acid residues in length. In some embodiments, the hinge region is 62 amino acid residues in length. Hinge regions can be subdivided into three distinct domains: upper, middle, and lower hinge domains. The FcRn antagonists of the instant disclosure can include all or any portion of a hinge region. In some embodiments, the hinge region is from an IgG1 antibody. In some embodiments, the hinge region comprises the amino acid sequence of EPKSCDKTHTCPPCP (SEQ ID NO: 23).

**[0050]** As used herein, the term "Fc region" refers to the portion of an immunoglobulin formed by the Fc domains of its two heavy chains. The Fc region can be a wild-type Fc region (native Fc region) or a variant Fc region. A native Fc region is homodimeric. The Fc region can be derived from any native immunoglobulin. In some embodiments, the Fc region is formed from an IgG heavy chain constant region. In some embodiments, the Fc region is formed from an IgG heavy chain constant region. In some embodiments, the IgG heavy chain constant region is an IgG1, IgG2, IgG3, or IgG4 heavy chain constant region. In some embodiments, the Fc region is formed from an IgG1 heavy chain constant region. In some embodiments, the IgG1 heavy chain constant region comprises a G1m1(a), G1m2(x), G1m3(f), or G1m17(z) allotype. *See, e.g.*, Jefferis and Lefranc (2009) mAbs 1(4):332-338, and de Taeye et al. (2020) Front Immunol. 11:740, incorporated herein by reference in their entirety.

**[0051]** As used herein, the term "variant Fc region" refers to an Fc region with one or more alteration(s) relative to a native Fc region. Alterations can include amino acid substitutions, additions and/or deletions, linkage of additional moieties, and/or alteration of the native glycans. The term encompasses heterodimeric Fc regions where each of the constituent Fc domains is different. The term also encompasses single chain Fc regions where the constituent Fc domains are linked together by a linker moiety.

**[0052]** As used herein, the term "FcRn binding fragment" refers to a portion of an Fc region that is sufficient to confer FcRn binding.

**[0053]** As used herein, the term "EU position" refers to the amino acid position in the EU numbering convention for the Fc region described in Edelman, GM et al., Proc. Natl. Acad. USA, 63, 78-85 (1969) and Rabat et al., in "Sequences of Proteins of Immunological Interest," U.S. Dept. Health and Human Services, 5th edition, 1991.

**[0054]** As used herein, the term "baseline" refers to a measurement (*e.g.*, IgG levels) in a patient (*e.g.*, in a patient's blood or urine) prior to the first administration (*e.g.*, intravenous or subcutaneous administration) of a treatment (*e.g.*, an FcRn antagonist).

**[0055]** As used herein, the term "autoantibody-mediated disease" refers to any disease or disorder in which the underlying pathology is caused, at least in part, by pathogenic IgG autoantibodies.

**[0056]** As used herein, the terms "treat," "treating," and "treatment" refer to therapeutic or preventative measures described herein. The methods of "treatment" employ administration of a polypeptide to a subject having a disease or disorder, or predisposed to having such a disease or disorder, in order to prevent, cure, delay, reduce the severity of, or ameliorate one or more symptoms of the disease or disorder or recurring disease or disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

**[0057]** As used herein, the term "effective amount" in the context of the administration of a therapy to a subject refers to the amount of a therapy that achieves a desired prophylactic or therapeutic effect.

**[0058]** As used herein, the terms "dose" or "dosing" refer to an amount of an agent administered to a subject in a single administration.

**[0059]** As used herein, the terms "fixed dose" or "flat dose" both refer to a dose that does not vary based upon a characteristic (*e.g.*, body mass, *e.g.*, within a set range; sex; age, *e.g.*, within a set range; *etc.*) of the subject.

**[0060]** As used herein, the term "biosimilar" refers to a biological product that is highly similar to and has no clinically meaningful differences from a reference product. As used herein, the term "reference product" refers to a biological product that has been approved for clinical use. In some embodiments, the reference product is approved in at least one of the U.S., Europe, China, or Japan. A biosimilar may have minor differences in clinically inactive components. A biosimilar

may include minor modifications in amino acid sequence when compared to the reference product, such as N- or C-terminal truncations that are not expected to change the biosimilar performance.

**[0061]** As used herein, "no clinically meaningful differences" is determined in terms of safety, purity, and potency. For example, a biosimilar is compared to and evaluated against a reference product to verify that the biosimilar has no clinically meaningful differences in terms of safety, purity, and potency from the reference product. In some embodiments, a determination of no clinically meaningful differences between a biosimilar and a reference product is based upon data derived from: (a) analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (b) animal studies (including, for example, assessment of toxicity); and/or (c) a clinical study or studies (including, for example, assessment of immunogenicity and pharmacokinetics or pharmacodynamics) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar. A biosimilar may be an interchangeable product that may be substituted for the reference product at a pharmacy without intervention of a prescribing healthcare professional. To meet a standard of "interchangeability," the biosimilar is expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar and the reference product is not greater than the risk of using the reference product without such alternation or switch. In some embodiments, the biosimilar utilizes the same mechanisms of action as the reference product for the proposed conditions of use, to the extent the mechanisms are known for the reference product. In some embodiments, the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biosimilar have been previously approved for the reference product. In some embodiments, the route of administration, the dosage form, and/or the strength of a biosimilar are the same as those of the reference product and the biosimilar is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biosimilar continues to be safe, pure, and potent.

**[0062]** As used herein, the term "clinically established result" means a result obtained in a subject as a result of a clinical trial following administration of an effective amount of therapeutic agent to the subject wherein the subject demonstrates a response that meets or exceeds one or more of the clinical endpoints described herein.

**[0063]** As used herein, the term "subject" or "patient" or "participant" includes any human or non-human animal. In an embodiment, the subject or patient or participant is a human or non-human mammal. In an embodiment, the subject or patient or participant is a human.

**[0064]** As used herein, the term "about" or "approximately" when referring to a measurable value, such as a dosage, encompasses variations of ±5% of a given value or range, as are appropriate to perform the methods disclosed herein.

**Primary Sjögren's Syndrome**

**[0065]** Primary Sjögren's syndrome (pSS) is a chronic, progressive autoimmune disease of unclear etiology, typically presented as an exocrinopathy. pSS is characterized by mononuclear inflammatory infiltrates and IgG plasma cells in salivary and lacrimal glands that lead to irreversible destruction of glandular tissue. Symptoms vary in type and intensity, but the burden of illness for many people with pSS is high. Although dry mouth and dry eyes are the most common symptoms, dryness can also occur in the nose, sinuses, ears, throat, skin, and, in women, the vagina. There is speculation that, in men with pSS, the prostate might be affected similarly to other organs. Patients may notice irritation, a gritty feeling, or painful burning in the eyes. Dry eyes are at increased risk for infection and susceptible to corneal damage if not treated. Dry mouth can lead to difficulty eating and swallowing dry foods, dental cavities, chipping, breaking, and loss of teeth. Dry mouth may also increase gingivitis and oral yeast infections that may cause pain and burning.

**[0066]** pSS can also affect the joints, muscles, nervous system (central nervous system and peripheral nervous system, including the autonomic nervous system), gastrointestinal tract (including the pancreas and liver), skin, blood vessels, lungs, and kidneys. Joint pain and stiffness with mild swelling are common, even in those without rheumatoid arthritis. Rashes may occur, including vasculitis, most commonly on the lower legs. Sun-sensitive rash is more common on the back, chest, face, and arms. Peripheral neuropathy can cause numbness and tingling, especially in the feet, and can frequently pre-date symptoms of dryness. Fatigue, cognitive dysfunction, and sleep abnormalities are frequently reported.

**[0067]** Diagnosis depends on a combination of symptoms, physical examination, blood tests, and special studies to look for objective evidence of dry eyes and dry mouth. Diagnosis of pSS cannot be based on symptoms alone because dry eyes and mouth are highly prevalent

symptoms in the general population and can be caused by many other conditions or by medications. Instead, diagnosis can be based upon tests used to assess decreases in tear or saliva production. For example, staining of the cornea and/or conjunctiva with vital dyes can detect and assess for damage to the outer surface of the eyes caused by dryness. Presence of autoantibodies that are often associated with pSS can also be used in diagnosis. Typical autoantibodies include one or more of anti-nuclear antibodies (ANA), anti-Ro/SS-A antibodies, anti-La/SS-B antibodies, and rheumatoid factor (RF). Biopsy of the minor salivary glands may also be used to make a diagnosis when autoantibodies are absent.

**[0068]** Currently, no systemic immunomodulating therapies are approved for pSS. Hydroxychloroquine may be helpful in some pSS patients to reduce joint pain, fatigue, or rash. Patients with systemic problems, such as fever, severe rash, lung disease, neurologic problems, or kidney involvement may be treated with corticosteroids (such as prednisone and methylprednisolone) and/or immunosuppressive drugs like methotrexate, azathioprine, mycophenolate mofetil, leflunomide, or cyclophosphamide. In addition, biological therapies, such as rituximab, may be used, especially in severe disease.

**[0069]** Dry eyes usually respond to artificial tears applied regularly during the day or to ointment applied at night. Other measures, such as plugging or blocking tear ducts by the ophthalmologist, can be used in more severe cases. Eye drops that reduce inflammation in the glands around the eyes, such as cyclosporine and lifitegrast, may significantly improve symptoms and decrease the need for artificial tears. Many patients benefit from using prescription medications that stimulate saliva flow, such as pilocarpine or cevimeline. If patients develop yeast infections, anti-fungal therapies may be needed. Medications that reduce gastric acid (such as proton-pump inhibitors and H2 blockers) may lessen symptoms of acid reflux.

**[0070]** There is a clear need for more effective treatments, given that the currently used medications treat only the symptoms of pSS and all have side effects which prohibit their continued use.

**FcRn Antagonists**

**[0071]** FcRn antagonists that are useful in the methods and uses provided herein include variant Fc regions that bind to and inhibit FcRn. Any Fc region can be altered to produce a variant Fc region for use in the methods disclosed herein. In an embodiment, the Fc region is an IgG Fc region (*e.g.*, a human IgG region). In an embodiment, the Fc region is selected from IgG1, IgG2,

IgG3, and IgG4. In an embodiment, the Fc region is an IgG1 Fc region (*e.g.*, a human IgG1 region). A variety of Fc region gene sequences (*e.g.*, human constant region gene sequences) are available in the form of publicly accessible deposits.

**[0072]** An Fc region can be further truncated or internally deleted to produce a minimal FcRn binding fragment thereof. The ability of an Fc-region fragment to bind to FcRn can be determined using any art recognized binding assay (*e.g.*, ELISA).

**[0073]** To enhance the manufacturability of the FcRn antagonists disclosed herein, it is preferable that the constituent Fc regions do not comprise any non-disulfide bonded cysteine residues. Accordingly, in an embodiment, the Fc regions do not comprise a free cysteine residue.

**[0074]** Any variant Fc region, or FcRn binding fragment thereof, that binds specifically to FcRn with increased affinity and reduced pH dependence relative to the native (*i.e.*, wild-type) Fc region can be used in the methods disclosed herein. In an embodiment, the variant Fc region comprises amino acid alterations, substitutions, insertions, and/or deletions that confer the desired characteristics. In some embodiments, the FcRn antagonist comprises a variant Fc region, or FcRn binding fragment thereof, which binds to FcRn with a higher affinity at pH 5.5 as compared to a corresponding wild-type Fc region. In some embodiments, the FcRn antagonist comprises or consists of a variant Fc region, or FcRn binding fragment thereof, which binds to FcRn with a higher affinity at pH 6.0 and/or at pH 7.4 as compared to a corresponding wild-type Fc region. In some embodiments, the FcRn antagonist comprises a variant Fc region, or FcRn binding fragment thereof, which binds to FcRn with a higher affinity at both acidic and neutral pH.

**[0075]** In some embodiments, the variant Fc region is derived from the Fc region of any native immunoglobulin. In some embodiments, the native immunoglobulin is a human immunoglobulin. In some embodiments, the immunoglobulin is IgG. In some embodiments, the immunoglobulin is human IgG. In some embodiments, the IgG is IgG1, IgG2, IgG3, or IgG4. In some embodiments, the human IgG is human IgG1, human IgG2, human IgG3, or human IgG4. In some embodiments, the variant Fc region varies from the human IgG1 Fc region. In some embodiments, the human IgG1 Fc region comprises a G1m1(a), G1m2(x), G1m3(f), or G1m17(z) allotype.

**[0076]** In an embodiment, the variant Fc region, or FcRn binding fragment thereof consists of two Fc domains.

**[0077]** In an embodiment, the variant Fc region comprises or consists of a first Fc domain and a second Fc domain which form a homodimer or heterodimer. In an embodiment, the first Fc

domain and/or the second Fc domain comprise amino acids Y, T, E, K, and F at EU positions 252, 254, 256, 433, and 434, respectively. In an embodiment, the first Fc domain and/or the second Fc domain comprise amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436, respectively.

**[0078]** In some embodiments, the FcRn antagonists disclosed herein comprise or consist of at least one Fc domain, wherein the amino acid sequence of the at least one Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 22, provided below.

**Table 1**

| **Amino Acid Sequence** | **SEQ ID NO:** |
|---|---|
| $X_1X_2X_3X_4X_5X_6$PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALKFHYTQKSLSLSPX$_7$X$_8$<br><br>wherein: $X_1$ is D or absent; $X_2$ is K or absent; $X_3$ is T or absent; $X_4$ is H or absent; $X_5$ is T or absent; $X_6$ is C or absent; $X_7$ is G or absent; $X_8$ is K or absent. | 22 |

**[0079]** In some embodiments, the FcRn antagonists disclosed herein comprise or consist of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 22.

**[0080]** In some embodiments, the FcRn antagonists disclosed herein comprise or consist of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence independently selected from the group consisting of SEQ ID NOs: 1-21. In some embodiments, the dimer is a heterodimer or a homodimer.

**Table 2**

| **Amino Acid Sequence** | **SEQ ID NO:** |
|---|---|
| CPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV | 1 |

| | |
|---|---|
| EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALKFHYTQKSLSLSPG | |
| **DKTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALKFHYTQKSLSLSPGK | 2 |
| **DKTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALKFHYTQKSLSLSPG | 3 |
| **C**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALKFHYTQKSLSLSPGK | 4 |
| **DKTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALKFHYTQKSLSLSP | 5 |
| **KTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALKFHYTQKSLSLSPGK | 6 |
| **KTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALKFHYTQKSLSLSPG | 7 |
| **KTHTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALKFHYTQKSLSLSP | 8 |
| **THTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALKFHYTQKSLSLSPGK | 9 |

| | |
|---|---|
| **THTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALKFHYTQKSLSLSPG | 10 |
| **THTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALKFHYTQKSLSLSP | 11 |
| **TC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSPGK | 12 |
| **TC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSPG | 13 |
| **TC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSP | 14 |
| PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALKFHYTQKSLSLSPGK | 15 |
| PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALKFHYTQKSLSLSPG | 16 |
| PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALKFHYTQKSLSLSP | 17 |
| **HTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA | 18 |

| | |
|---|---|
| VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSPGK | |
| **HTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSPG | 19 |
| **HTC**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALKFHYTQKSLSLSP | 20 |
| **C**PPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALKFHYTQKSLSLSP | 21 |

**[0081]** In an embodiment, the first Fc domain and/or the second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NOs: 1, 2, 3, and 4. In an embodiment, the first Fc domain and the second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NOs: 1, 2, 3, and 4.

**[0082]** In some embodiments, the FcRn antagonist comprises a population of FcRn antagonist molecules. In some embodiments, a FcRn antagonist comprising a first Fc domain and a second Fc domain comprising an amino acid sequence independently selected from the group consisting of SEQ ID NOs: 1, 2, 3, and 4 is the predominant FcRn antagonist molecule in the population of FcRn antagonist molecules. In some embodiments, the predominant FcRn antagonist molecule makes up at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% of the population of FcRn antagonist molecules.

**[0083]** In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region comprises the amino acid sequence of SEQ ID NO: 1. In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence of SEQ ID NO: 1.

**[0084]** In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region comprises the amino acid sequence of SEQ ID NO: 2. In an embodiment, the amino acid

sequence of the Fc domains of the variant Fc region consists of the amino acid sequence of SEQ ID NO: 2.

**[0085]** In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region comprises the amino acid sequence of SEQ ID NO: 3. In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence of SEQ ID NO: 3.

**[0086]** In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region comprises the amino acid sequence of SEQ ID NO: 4. In an embodiment, the amino acid sequence of the Fc domains of the variant Fc region consists of the amino acid sequence of SEQ ID NO: 4.

**[0087]** In certain embodiments, the variant Fc region is a heterodimer, where the constituent Fc domains are different from each other. Methods of producing Fc heterodimers are known in the art (*see, e.g.*, US 8,216,805, which is incorporated by reference herein in its entirety). In an embodiment, the FcRn antagonist consists of a variant Fc region, wherein the variant Fc region consists of two Fc domains which form a heterodimer, wherein the amino acid sequence of each of the Fc domains is independently selected from SEQ ID NOs: 1, 2, 3, or 4. In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a heterodimer, wherein the amino acid sequence of the first Fc domain consists of or comprises the amino acid sequence of SEQ ID NO: 1 and the amino acid sequence of the second Fc domain consists of or comprises the amino acid sequence of SEQ ID NOs: 2, 3, or 4. In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a heterodimer, wherein the amino acid sequence of the first Fc domain consists of or comprises the amino acid sequence of SEQ ID NO: 2 and the amino acid sequence of the second Fc domain consists of or comprises the amino acid sequence of SEQ ID NOs: 1, 3, or 4. In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a heterodimer, wherein the amino acid sequence of the first Fc domain consists of or comprises the amino acid sequence of SEQ ID NO: 3 and the amino acid sequence of the second Fc domain consists of or comprises the amino acid sequence of SEQ ID NOs: 1, 2, or 4. In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a heterodimer, wherein the amino acid sequence of the first Fc domain

consists of or comprises the amino acid sequence of SEQ ID NO: 4 and the amino acid sequence of the second Fc domain consists of or comprises the amino acid sequence of SEQ ID NOs: 1, 2, or 3.

**[0088]** In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a homodimer, wherein the amino acid sequence of each of the Fc domains consists of or comprises the amino acid sequence of SEQ ID NO: 1.

**[0089]** In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a homodimer, wherein the amino acid sequence of each of the Fc domains consists of or comprises the amino acid sequence of SEQ ID NO: 2.

**[0090]** In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a homodimer, wherein the amino acid sequence of each of the Fc domains consists of or comprises the amino acid sequence of SEQ ID NO: 3.

**[0091]** In an embodiment, the FcRn antagonist consists of or comprises a variant Fc region, wherein the variant Fc region consists of or comprises two Fc domains which form a homodimer, wherein the amino acid sequence of each of the Fc domains consists of or comprises the amino acid sequence of SEQ ID NO: 4.

**[0092]** In some embodiments, the FcRn antagonist comprises glycanation on one or both of the Fc domains. In some embodiments, the FcRn antagonist molecules comprise glycanation at EU position 297 on one or both of the Fc domains. In some embodiments, the glycanation comprises an N-glycan. In some embodiments, the N-glycan comprises a G0F N-glycan, G1F N-glycan, G2F N-glycan, or G0 N-glycan.

**[0093]** In some embodiments, FcRn antagonist comprises or consists of a population of FcRn antagonists, wherein at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, or at least 57% of the population of Fc domains of the FcRn antagonists comprise galactose. In some embodiments, the population comprises or consists of FcRn antagonists, wherein at least 88%, at least 89%, at least 90%, at

least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% of the population of Fc domains of the FcRn antagonists comprise fucose.

**[0094]** In some embodiments, the FcRn antagonist lacks an amino acid at EU position 441 of one or both Fc domains. In some embodiments, the FcRn antagonist comprises glycine and lysine at EU positions 440 and 441, respectively. In some embodiments, the FcRn antagonist lacks amino acids at EU positions 440 and 441. In some embodiments, the FcRn antagonist comprises amidated proline at EU position 439. In some embodiments, the FcRn antagonist lacks amino acids at EU positions 440 and 441 and comprise amidated proline at EU position 439.

**[0095]** In some embodiments, the FcRn antagonist comprises aspartate, lysine, threonine, histidine, threonine, and cysteine at EU positions 221, 222, 223, 224, 225, and 226, respectively. In some embodiments, the FcRn antagonist lacks an amino acid at EU positions 221, and comprises lysine, threonine, histidine, threonine, and cysteine at EU positions 222, 223, 224, 225, and 226, respectively. In some embodiments, the FcRn antagonist lacks amino acids at EU positions 221 and 222, and comprises threonine, histidine, threonine, and cysteine at EU positions 223, 224, 225, and 226, respectively. In some embodiments, the FcRn antagonist lacks amino acids at EU positions 221-224, and comprises threonine and cysteine at EU positions 225 and 226, respectively. In some embodiments, the FcRn antagonist lacks amino acids at EU positions 221, 222, 223, 224, 225, and 226.

**[0096]** In some embodiments, the FcRn antagonist is a population of FcRn antagonist molecules. In some embodiments, the population of FcRn antagonist molecules comprises or consists of multiple subpopulations of FcRn antagonist molecules. In some embodiments, the population of FcRn antagonist molecules comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 subpopulations.

**[0097]** In some embodiments, a first subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3.

**[0098]** In some embodiments, a second subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain

comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 3 and 13, respectively.

**[0099]** In some embodiments, a third subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 3 and 10, respectively.

**[00100]** In some embodiments, a fourth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3, and wherein two asparagine residues in each FcRn antagonist molecule in the fourth subpopulation are deaminated.

**[00101]** In some embodiments, a fifth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3, and wherein one asparagine residue in each FcRn antagonist molecule in the fifth subpopulation are deaminated.

**[00102]** In some embodiments, a sixth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 2 and 3, respectively.

**[00103]** In some embodiments, a seventh subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3, and wherein one

methionine residue or one tryptophan residue in each FcRn antagonist molecule in the seventh subpopulation is oxidized.

**[00104]** In some embodiments, an eighth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 2.

**[00105]** In some embodiments, a ninth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 3 and 7, respectively.

**[00106]** In some embodiments, a tenth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NOs: 2 and 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the tenth subpopulation is oxidized.

**[00107]** In some embodiments, an eleventh subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 3, and wherein two amino acid residues, independently selected from a methionine residue or a tryptophan residue, in each FcRn antagonist molecule in the eleventh subpopulation is oxidized.

**[00108]** In some embodiments, a first subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 3.

**[00109]** In some embodiments, a second subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NOs: 3 and 13, respectively.

**[00110]** In some embodiments, a third subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NOs: 3 and 10, respectively.

**[00111]** In some embodiments, a fourth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 3, and wherein two asparagine residues in each FcRn antagonist molecule in the fourth subpopulation are deaminated.

**[00112]** In some embodiments, a fifth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 3, and wherein one asparagine residue in each FcRn antagonist molecule in the fifth subpopulation is deaminated.

**[00113]** In some embodiments, a sixth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NOs: 2 and 3, respectively.

**[00114]** In some embodiments, a seventh subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 3, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the seventh subpopulation is oxidized.

**[00115]** In some embodiments, an eighth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 2.

**[00116]** In some embodiments, a ninth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NOs: 3 and 7, respectively.

**[00117]** In some embodiments, a tenth subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NOs: 2 and 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the tenth subpopulation is oxidized.

**[00118]** In some embodiments, an eleventh subpopulation of FcRn antagonist molecules comprises or consists of a variant Fc region comprising or consisting of a dimer of a first Fc domain and a second Fc domain, wherein the amino acid sequence of both the first and second Fc domain comprises or consists of the amino acid sequence of SEQ ID NO: 3, and wherein two amino acid residues, independently selected from a methionine residue or a tryptophan residue in each FcRn antagonist molecule in the eleventh subpopulation is oxidized.

**[00119]** In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with one of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with two of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with three of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with four of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with five of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with six of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with seven

of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with eight of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with nine of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations. In some embodiments, the population of FcRn antagonist molecules comprises or consists of the first subpopulation combined with all of the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh subpopulations.

**[00120]** In some embodiments, the population comprises or consists of the first and second subpopulations. In some embodiments, the population comprises or consists of the first and third subpopulations. In some embodiments, the population comprises or consists of the first and fourth subpopulations. In some embodiments, the population comprises or consists of the first and fifth subpopulations. In some embodiments, the population comprises or consists of the first and sixth subpopulations. In some embodiments, the population comprises or consists of the first and seventh subpopulations. In some embodiments, the population comprises or consists of the first and eighth subpopulations. In some embodiments, the population comprises or consists of the first and ninth subpopulations. In some embodiments, the population comprises or consists of the first and tenth subpopulations. In some embodiments, the population comprises or consists of the first and eleventh subpopulations. In some embodiments, the populations listed above further comprise or consist of 1, 2, 3, 4, 5, 6, 7, 8, or 9 additional subpopulations. In some embodiments, these additional subpopulations are one or more of those described above.

**[00121]** In some embodiments, the population comprises or consists of the first and seventh, ninth, or eleventh subpopulations. In some embodiments, the population comprises or consists of the first, seventh, ninth, and eleventh subpopulations.

**[00122]** In some embodiments, the first subpopulation makes up at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90% of the population of FcRn antagonist molecules. In some embodiments, the first subpopulation makes up about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, or about 90% of the population of FcRn antagonist molecules. In some embodiments, the first subpopulation makes up 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% of the population of FcRn antagonist molecules.

In some embodiments, the first subpopulation makes up 40%-90%, 50%-80%, or 55%-70% of the population of FcRn antagonist molecules. In some embodiments, the first subpopulation makes up 56.9%-68.3% or 59.5%-67.9% of the population of FcRn antagonist molecules.

**[00123]** In some embodiments, the second subpopulation makes up less than 3.0%, less than 2.5%, less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the second subpopulation makes up about 3.0%, about 2.5%, about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the second subpopulation makes up 3.0%, 2.5%, 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the second subpopulation makes up 0.5%-3.0%, 1.0%-2.5%, or 1.0%-2.0% of the population of FcRn antagonist molecules. In some embodiments, the second subpopulation makes up 0.8%-2.0% or 0.8%-2.1% of the population of FcRn antagonist molecules.

**[00124]** In some embodiments, the third subpopulation makes up less than 3.0%, less than 2.5%, less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the third subpopulation makes up about 3.0%, about 2.5%, about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the third subpopulation makes up 3.0%, 2.5%, 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the third subpopulation makes up 0.5%-3.0%, 1.0%-2.5%, or 1.0%-2.0% of the population of FcRn antagonist molecules. In some embodiments, the third subpopulation makes up 1.1%-2.1% or 1.0%-1.9% of the population of FcRn antagonist molecules.

**[00125]** In some embodiments, the fourth subpopulation makes up less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% of the population of FcRn antagonist molecules. In some embodiments, the fourth subpopulation makes up about 5%, about 4%, about 3%, about 2%, or about 1% of the population of FcRn antagonist molecules. In some embodiments, the fourth subpopulation makes up 5%, 4%, 3%, 2%, or 1% of the population of FcRn antagonist molecules. In some embodiments, the fourth subpopulation makes up 1%-5%, 2%-4%, or 2%-3% of the population of FcRn antagonist molecules. In some embodiments, the fourth subpopulation makes up 2.1%-3.2% or 2.0%-3.1% of the population of FcRn antagonist molecules.

**[00126]** In some embodiments, the fifth subpopulation makes up less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, or less than 5% of the population of FcRn antagonist molecules. In some embodiments, the fifth subpopulation makes up

about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, about 6%, or about 5% of the population of FcRn antagonist molecules. In some embodiments, the fifth subpopulation makes up 12%, 11%, 10%, 9%, 8%, 7%, 6%, or 5% of the population of FcRn antagonist molecules. In some embodiments, the fifth subpopulation makes up 5%-12%, 6%-10%, or 7%-8% of the population of FcRn antagonist molecules. In some embodiments, the fifth subpopulation makes up 6.8%-9.4% or 6.9%-8.7% of the population of FcRn antagonist molecules.

**[00127]** In some embodiments, the sixth subpopulation makes up less than 17%, less than 16%, less than 15%, less than 14%, less than 13%, less than 12%, less than 11%, less than 10%, less than 9%, less than 8%, less than 7%, or less than 6% of the population of FcRn antagonist molecules. In some embodiments, the sixth subpopulation makes up about 17%, about 16%, about 15%, about 14%, about 13%, about 12%, about 11%, about 10%, about 9%, about 8%, about 7%, or about 6% of the population of FcRn antagonist molecules. In some embodiments, the sixth subpopulation makes up 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, or 6% of the population of FcRn antagonist molecules. In some embodiments, the sixth subpopulation makes up 7%-17%, 10%-15%, or 11%-12% of the population of FcRn antagonist molecules. In some embodiments, the sixth subpopulation makes up 7.0%-14.0% or 10.0%-14.4% of the population of FcRn antagonist molecules.

**[00128]** In some embodiments, the seventh subpopulation makes up less than 6.0%, less than 5.5%, less than 5.0%, less than 4.5%, less than 4.0%, less than 3.5%, less than 3.0%, less than 2.5%, less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the seventh subpopulation makes up about 6.0%, about 5.5%, about 5.0%, about 4.5%, about 4.0%, about 3.5%, about 3.0%, about 2.5%, about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the seventh subpopulation makes up 6.0%, 5.5%, 5.0%, 4.5%, 4.0%, 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the seventh subpopulation makes up 0.5%-5.5%, 1.0%-3.0%, or 1.5%-2.5% of the population of FcRn antagonist molecules. In some embodiments, the seventh subpopulation makes up 1.5%-5.5% or 1.4%-4.9% of the population of FcRn antagonist molecules.

**[00129]** In some embodiments, the eighth subpopulation makes up less than 7.5%, less than 7.0%, less than 6.5%, less than 6.0%, less than 5.5%, less than 5.0%, less than 4.5%, less than 4.0%, less than 3.5%, less than 3.0%, or less than 2.5% of the population of FcRn antagonist molecules. In some embodiments, the eighth subpopulation makes up about 7.5%, about 7.0%,

about 6.5%, about 6.0%, about 5.5%, about 5.0%, about 4.5%, about 4.0%, about 3.5%, about 3.0%, or about 2.5% of the population of FcRn antagonist molecules. In some embodiments, the eighth subpopulation makes up 7.5%, 7.0%, 6.5%, 6.0%, 5.5%, 5.0%, 4.5%, 4.0%, 3.5%, 3.0%, or 2.5% of the population of FcRn antagonist molecules. In some embodiments, the eighth subpopulation makes up 2.5%-7.5%, 3.0%-5.0%, or 3.5%-4.5% of the population of FcRn antagonist molecules. In some embodiments, the eighth subpopulation makes up 2.9%-7.4% or 3.0%-6.3% of the population of FcRn antagonist molecules.

**[00130]** In some embodiments, the ninth subpopulation makes up less than 3.5%, less than 3.0%, less than 2.5%, less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the ninth subpopulation makes up about 3.5%, about 3.0%, about 2.5%, about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the ninth subpopulation makes up 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the ninth subpopulation makes up 0.5%-3.5%, 1.5%-2.0%, or 1.0%-1.5% of the population of FcRn antagonist molecules. In some embodiments, the ninth subpopulation makes up 0.4%-3.2% or 0.5%-2.6% of the population of FcRn antagonist molecules.

**[00131]** In some embodiments, the tenth subpopulation makes up less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the tenth subpopulation makes up about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the tenth subpopulation makes up 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the tenth subpopulation makes up 0.5%-2.0%, 0.5%-1.5%, or 1.0%-1.5% of the population of FcRn antagonist molecules.

**[00132]** In some embodiments, the eleventh subpopulation makes up less than 2.0%, less than 1.5%, less than 1%, or less than 0.5% of the population of FcRn antagonist molecules. In some embodiments, the eleventh subpopulation makes up about 2.0%, about 1.5%, about 1%, or about 0.5% of the population of FcRn antagonist molecules. In some embodiments, the eleventh subpopulation makes up 2.0%, 1.5%, 1%, or 0.5% of the population of FcRn antagonist molecules. In some embodiments, the eleventh subpopulation makes up 0.5%-2.0%, 0.5%-1.5%, or 1.0%-1.5% of the population of FcRn antagonist molecules.

**[00133]** In some embodiments, the population of FcRn antagonist molecules comprises one or more of the FcRn antagonists described herein. In some embodiments, the FcRn antagonist is

any of those described in International Patent Application No. PCT/IB2023/000696, filed on November 14, 2023, incorporated herein by reference in its entirety. In some embodiments, the FcRn antagonist is a population of FcRn antagonists as described in International Patent Application No. PCT/IB2023/000696, filed on November 14, 2023, incorporated herein by reference in its entirety.

**[00134]** In an embodiment, the FcRn antagonist is efgartigimod (CAS Registry No. 1821402-21-4). The term "efgartigimod" as used herein is interchangeable with "efgartigimod alfa." In some embodiments, efgartigimod is efgartigimod alfa-fcab.

**Pharmaceutical Compositions**

**[00135]** In an aspect, the instant disclosure provides pharmaceutical compositions comprising an FcRn antagonist for use in methods of treating pSS.

**[00136]** In an embodiment, the FcRn antagonist is efgartigimod. Efgartigimod (ARGX-113) is a modified human immunoglobulin (Ig) gamma (IgG) 1-derived Fc of the za allotype that binds with nanomolar affinity to human FcRn. Efgartigimod encompasses the IgG1 Fc-region and has been engineered using ABDEG™ technology to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of efgartigimod at both acidic and physiological pH results in a blockage of FcRn-mediated recycling of IgG.

**[00137]** Efgartigimod is a prescription medicine registered as VYVGART®, which is approved in the United States and in Europe for the treatment of adults with gMG who are anti-AChR antibody positive, and in Japan for the treatment of adults with gMG who do not have sufficient response to steroids or non-steroidal immunosuppressive therapies (ISTs). Efgartigimod is under development for both the intravenous (IV) and subcutaneous (SC) administration route.

**[00138]** For IV administration, in certain embodiments, efgartigimod may be administered in a formulation comprising sodium phosphate, sodium chloride, L-arginine hydrochloride, and polysorbate 80. In certain embodiments, efgartigimod may be administered in a formulation comprising about 25 mM sodium phosphate, about 100 mM sodium chloride, and about 150 mM L-arginine hydrochloride (pH 6.7), with about 0.02% (w/v) polysorbate 80. In certain embodiments, efgartigimod may be administered in a formulation comprising 25 mM sodium phosphate, 100 mM sodium chloride, and 150 mM L-arginine hydrochloride (pH 6.7), with 0.02% (w/v) polysorbate 80. In certain embodiments, efgartigimod may be administered in a formulation

comprising about 25 mM sodium phosphate, about 100 mM sodium chloride, and about 150 mM L-arginine hydrochloride (pH 6.7), with about 0.02% (w/v) polysorbate 80, via intravenous infusion in a total volume of about 250 mL over a period of about 2 hours. In certain embodiments, efgartigimod may be administered in a formulation comprising 25 mM sodium phosphate, 100 mM sodium chloride, and 150 mM L-arginine hydrochloride (pH 6.7), with 0.02% (w/v) polysorbate 80, via intravenous infusion in a total volume of 250 mL over a period of 2 hours. *See, e.g.*, WO2019110823A1, which is incorporated by reference herein in its entirety.

**[00139]** In certain embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising about 25 mM sodium phosphate, about 100 mM sodium chloride, and about 150 mM L-arginine hydrochloride with a pH of about 6.7, with about 0.02% (w/v) polysorbate 80, diluted for intravenous infusion to a total volume of about 125 mL over a period of about 1 hour. In certain embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising 25 mM sodium phosphate, 100 mM sodium chloride, and 150 mM L-arginine hydrochloride with a pH of 6.7, with 0.02% (w/v) polysorbate 80, diluted for intravenous infusion to a total volume of 125 mL over a period of 1 hour.

**[00140]** In certain embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising about 4 mM sodium phosphate, about 146 mM sodium chloride, about 24 mM L-arginine, and about 0.0032% (w/v) polysorbate 80, with a pH of about 6.7. This formulation is administered via intravenous infusion in a total volume of about 125 mL over a period of about 1 hour. In certain embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising 4 mM sodium phosphate, 146 mM sodium chloride, 24 mM L-arginine, and 0.0032% (w/v) polysorbate 80, with a pH of 6.7. This formulation is administered via intravenous infusion in a total volume of 125 mL over a period of 1 hour.

**[00141]** In certain embodiments, efgartigimod is administered via IV infusion and is provided in a sterile, colorless, clear concentrate solution at a concentration of about 20 mg/mL. In certain embodiments, efgartigimod is administered via IV infusion and is provided in a sterile, colorless, clear concentrate solution at a concentration of 20 mg/mL.

**[00142]** In certain embodiments, efgartigimod is administered via IV infusion and is provided in a vial (*e.g.*, a single-dose vial). In certain embodiments, a vial of efgartigimod contains about 400 mg of efgartigimod at a concentration of about 20 mg/mL. In certain embodiments, a vial of efgartigimod contains 400 mg of efgartigimod at a concentration of 20 mg/mL. In certain

embodiments, each mL of solution in a vial of efgartigimod contains about 31.6 mg L-arginine hydrochloride, about 0.2 mg polysorbate 80, about 5.8 mg sodium chloride, about 2.4 mg sodium phosphate dibasic anhydrous, about 1.1 mg sodium phosphate monobasic monohydrate, and water for injection, USP, at a pH of about 6.7. In certain embodiments, each mL of solution in a vial of efgartigimod contains 31.6 mg L-arginine hydrochloride, 0.2 mg polysorbate 80, 5.8 mg sodium chloride, 2.4 mg sodium phosphate dibasic anhydrous, 1.1 mg sodium phosphate monobasic monohydrate, and water for injection, USP, at a pH of 6.7.

**[00143]** In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of about 10 mg/kg as an IV infusion. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of about 10 mg/kg as an IV infusion over about one hour. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of about 10 mg/kg as an IV infusion over about one hour once weekly. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of about 10 mg/kg as an IV infusion over about one hour once weekly for about 4 weeks. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of 10 mg/kg as an IV infusion. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of 10 mg/kg as an IV infusion over one hour. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of 10 mg/kg as an IV infusion over one hour once weekly. In certain embodiments, for patients weighing under 120 kg, efgartigimod is administered at a dose of 10 mg/kg as an IV infusion over one hour once weekly for 4 weeks. In certain embodiments, for patients weighing 120 kg or more, efgartigimod is administered at a dose of about 1200 mg per IV infusion. In certain embodiments, for patients weighing 120 kg or more, efgartigimod is administered at a dose of 1200 mg per IV infusion.

**[00144]** For SC administration, in certain embodiments, efgartigimod may be administered alone. Alternatively, for SC administration, in certain embodiments, efgartigimod may be administered co-formulated with hyaluronidase, for example, rHuPH20. The co-formulated material will allow SC dosing of larger volumes.

**[00145]** In some embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising about 20 mM L-histidine, about 100 mM sodium chloride, about 60 mM sucrose, about 10 mM L-methionine, and about 0.04% (w/v) polysorbate 20, wherein the formulation has a pH of about 6.0. In some embodiments, the formulation comprises about 180 mg/mL efgartigimod. In some embodiments, efgartigimod may be

administered in a formulation comprising an aqueous solution comprising 20 mM L-histidine, 100 mM sodium chloride, 60 mM sucrose, 10 mM L-methionine, and 0.04% (w/v) polysorbate 20, wherein the formulation has a pH of 6.0. In some embodiments, the formulation comprises 180 mg/mL efgartigimod.

**[00146]** In some embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising about 20 mM L-histidine, about 50 mM L-arginine, about 100 mM sodium chloride, about 60 mM sucrose, about 10 mM L-methionine, and about 0.04 (w/v) polysorbate 80, wherein the formulation has a pH of about 6.0. In some embodiments, the formulation comprises about 200 mg/mL efgartigimod. In some embodiments, efgartigimod may be administered in a formulation comprising an aqueous solution comprising 20 mM L-histidine, 50 mM L-arginine, 100 mM sodium chloride, 60 mM sucrose, 10 mM L-methionine, and 0.04 (w/v) polysorbate 80, wherein the formulation has a pH of 6.0. In some embodiments, the formulation comprises 200 mg/mL efgartigimod.

**[00147]** rHuPH20 is the active ingredient of Halozyme's commercial product HYLENEX® recombinant (hyaluronidase human injection), referred to as HYLENEX®, which was approved by FDA for marketed use in the U.S. in December 2005. HYLENEX® is a tissue permeability modifier indicated as an adjuvant in SC fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in SC urography, for improving resorption of radiopaque agents.

**[00148]** rHuPH20 is a recombinant enzyme human hyaluronidase produced by genetically engineered Chinese hamster ovary (CHO) cells containing a deoxyribonucleic plasmid encoding a soluble fragment of human hyaluronidase (posterior head protein 20 [PH20]).

**[00149]** The HZ202 rHuPH20 DS is currently registered in HYLENEX® and other biologic drug products co-formulated with rHuPH20 DS. As such, in certain embodiments HZ202 rHuPH20 DS is used in the efgartigimod / rHuPH20 co-formulated product for SC administration (*i.e.*, efgartigimod PH20 SC).

**[00150]** Provided in the co-formulations, combinations, uses and methods herein are soluble hyaluronidases. Soluble hyaluronidases include any that, upon expression, are secreted from a cell and exist in soluble form. Such soluble hyaluronidases include, but are not limited to, bacterial soluble hyaluronidases, non-human soluble hyaluronidases, such as bovine PH20 and ovine PH20, human soluble PH20, and variants thereof. Generally soluble forms of PH20 are produced using protein expression systems that facilitate correct N-glycosylation to ensure the polypeptide retains

activity, since glycosylation is important for the catalytic activity and stability of hyaluronidases. Such cells include, for example Chinese Hamster Ovary (CHO) cells (*e.g.*, DG44 CHO cells).

**[00151]** In some embodiments, rHuPH20 refers to the composition produced upon expression in a cell, such as a CHO cell, of nucleic acid encoding residues 36-482 of SEQ ID NO: 24, generally linked to the native or a heterologous signal sequence (residues 1-35 of SEQ ID NO: 24). rHuPH20 is produced by expression of a nucleic acid molecule, such as encoding amino acids 1-482 (set forth in SEQ ID NO: 24) in a mammalian cell. Translational processing removes the 35 amino acid signal sequence. As produced in the culture medium there is heterogeneity at the C-terminus such that the product, designated rHuPH20, includes a mixture of species that can include any one or more of the polypeptides 36-480, 36-481, and 36-482 of SEQ ID NO: 24, and some shorter polypeptides, in various abundance. Typically, rHuPH20 is produced in cells that facilitate correct N-glycosylation to retain activity, such as CHO cells (*e.g.*, DG44 CHO cells). In some embodiments, one of the most abundant species is the 446 amino acid polypeptide corresponding to residues 36-481 of SEQ ID NO: 24. In some embodiments, rHuPH20 refers to polypeptides that are soluble or secreted upon expression in a mammalian cell and have at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more sequence identity with residues 36-482 of SEQ ID NO: 24. In some embodiments, the rHuPH20 is the 447 amino acid polypeptide of SEQ ID NO: 25.

**Table 3. Exemplary hyaluronidase sequences**

| SEQ ID NO: | Amino Acid Sequence |
|---|---|
| 24 | MGVLKFKHIFFRSFVKSSGVSQIVFTFLLIPCCLTLNFRAPPVIPNVPF<br>LWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRINATGQGVTIFYVDRL<br>GYYPYIDSITGVTVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM<br>AVIDWEEWRPTWARNWKPKDVYKNRSIELVQQQNVQLSLTEATE<br>KAKQEFEKAGKDFLVETIKLGKLLRPNHLWGYYLFPDCYNHHYKK<br>PGYNGSCFNVEIKRNDDLSWLWNESTALYPSIYLNTQQSPVAATLY<br>VRNRVREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYT<br>FGETVALGASGIVIWGTLSIMRSMKSCLLLDNYMETILNPYIINVTL<br>AAKMCSQVLCQEQGVCIRKNWNSSDYLHLNPDNFAIQLEKGGKFT<br>VRGKPTLEDLEQFSEKFYCSCYSTLSCKEKADVKDTDAVDVCIADG<br>VCIDAFLKPPMETEEPQIFYNASPSTLSATMFIVSILFLIISSVASL |
| 25 | LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSLFSFIGSPRIN<br>ATGQGVTIFYVDRLGYYPYIDSITGVTVNGGIPQKISLQDHLDKAK<br>KDITFYMPVDNLGMAVIDWEEWRPTWARNWKPKDVYKNRSIELV<br>QQQNVQLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLWG<br>YYLFPDCYNHHYKKPGYNGSCPNVEIKRNDDLSWLWNESTALYPS |

| | |
|---|---|
| | IYLNTQQSPVAATLYVRNRVREAIRVSKIPDAKSPLPVFAYTRIVFT<br>DQVLKFLSQDELVYTFGETVALGASGIVIWGTLSIMRSMKSCLLLD<br>NYMETILNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSSDYLHL<br>NPDNFAIQLEKGGKFTVRGKPTLEDLEQFSEKFYCSCYSTLSCKEK<br>ADVKDTDAVDVCIADGVCIDAFLKPPMETEEPQIFY |

**[00152]** In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 20 mg to about 20,000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 200 mg to about 20,000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 300 mg to about 6000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 750 mg to about 3000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 1000 mg to about 2500 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from about 1000 mg to about 2000 mg.

**[00153]** In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 20 mg to 20,000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 200 mg to 20,000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 300 mg to 6000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 750 mg to 3000 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 1000 mg to 2500 mg. In some embodiments, the pharmaceutical formulation comprises an FcRn antagonist in an amount from 1000 mg to 2000 mg.

**[00154]** In some embodiments, the pharmaceutical formulation comprises about 1000 mg or about 2000 mg of an FcRn antagonist. In some embodiments, the pharmaceutical formulation comprises 1000 mg or 2000 mg of an FcRn antagonist. In some embodiments, the FcRn antagonist is efgartigimod.

**[00155]** In some embodiments, the pharmaceutical formulation comprises efgartigimod in an amount from about 800 mg to about 1200 mg. In some embodiments, the pharmaceutical formulation comprises efgartigimod in an amount from 800 mg to 1200 mg.

**[00156]** In some embodiments, the pharmaceutical formulation comprises about 1000 mg efgartigimod. In some embodiments, the pharmaceutical formulation comprises 1000 mg efgartigimod.

**[00157]** In some embodiments, the pharmaceutical formulation comprises from about 10 mg/mL to about 200 mg/mL efgartigimod. In some embodiments, the pharmaceutical formulation comprises from 10 mg/mL to 200 mg/mL efgartigimod.

**[00158]** In some embodiments, the pharmaceutical formulation comprises about 20 mg/mL efgartigimod. In some embodiments, the pharmaceutical formulation comprises 20 mg/mL efgartigimod.

**[00159]** In some embodiments, the pharmaceutical formulation comprises about 180 mg/mL efgartigimod. In some embodiments, the pharmaceutical formulation comprises 180 mg/mL efgartigimod.

**[00160]** In some embodiments, the pharmaceutical formulation further comprises hyaluronidase. In some embodiments, the hyaluronidase is recombinant human hyaluronidase PH20 (rHuPH20).

**[00161]** The hyaluronidase can be present in the pharmaceutical formulation in any suitable amount. In an embodiment, the amount of hyaluronidase enzyme is from about 1000 U/mL to about 3000 U/mL. In an embodiment, the amount of hyaluronidase enzyme is about 1000 U/mL, about 1500 U/mL, about 2000 U/mL, about 2500 U/mL, or about 3000 U/mL. In an embodiment, the amount of hyaluronidase enzyme is 2000 U/mL.

**[00162]** In some embodiments, the rHuPH20 is present in the pharmaceutical formulation in an amount of about 11,000 U. In some embodiments, the rHuPH20 is present in the pharmaceutical formulation in an amount of 11,000 U.

**[00163]** In some embodiments, the pharmaceutical formulation comprises at least about 5 U to at least about 100,000 U of an endoglycosidase hydrolase enzyme. In some aspects, the pharmaceutical formulation comprises at least about 5 U, at least about 10 U, at least about 20 U, at least about 30 U, at least about 40 U, at least about 50 U, at least about 75 U, at least about 100 U, at least about 200 U, at least about 300 U, at least about 400 U, at least about 500 U, at least about 750 U, at least about 1000 U, at least about 2000 U, at least about 3000 U, at least about 4000 U, at least about 5000 U, at least about 6000 U, at least about 7000 U, at least about 8000 U, at least about 9000 U, at least about 10,000 U, at least about 20,000 U, at least about 30,000 U, at least about 40,000 U, at least about 50,000 U, at least about 60,000 U, at least about 70,000 U, at

least about 80,000 U, at least about 90,000 U, or at least about 100,000 U of an endoglycosidase hydrolase enzyme.

**[00164]** In some embodiments, the pharmaceutical formulation comprises about 20,000 U of an endoglycosidase hydrolase enzyme. In some embodiments, the pharmaceutical formulation comprises at least about 500 U/mL to at least about 5000 U/mL of an endoglycosidase hydrolase enzyme. In some embodiments, the pharmaceutical formulation comprises at least about 1500 U/mL, at least about 1600 U/mL, at least about 1700 U/mL, at least about 1800 U/mL, at least about 1900 U/mL, at least about 2000 U/mL, at least about 2100 U/mL, at least about 2200 U/mL, at least about 2300 U/mL, at least about 2400 μM, at least about 2500 μM, at least about 3000 μM, at least about 3500 μM, at least about 4000 μM, at least about 4500 U/mL, or at least about 5000 U/mL of an endoglycosidase hydrolase enzyme. In some embodiments, the pharmaceutical formulation comprises about 2000 U/mL of an endoglycosidase hydrolase enzyme.

**[00165]** In some embodiments, the endoglycosidase hydrolase enzyme cleaves hyaluronic acid at a hexosaminidic β (1–4) or (1–3) linkage. In some embodiments, the endoglycosidase hydrolase enzyme comprises a catalytic domain of hyaluronidase PH-20 (HuPH20), HYAL1, HYAL2, HYAL3, HYAL4, or HYALPS1. In some embodiments, the endoglycosidase hydrolase enzyme comprises an amino acid sequence having at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence identity to amino acids 36-490 of SEQ ID NO: 24. In some embodiments, the endoglycosidase hydrolase enzyme comprises a hyaluronidase. In some embodiments, the endoglycosidase hydrolase enzyme comprises a hyaluronidase selected from the group consisting of HuPH20, HYAL1, HYAL2, HYAL3, HYAL4, any variant, and any isoform thereof. In some embodiments, the endoglycosidase hydrolase enzyme comprises rHuPH20 or a fragment thereof.

**[00166]** In some embodiments, the endoglycosidase hydrolase enzyme comprises a modified hyaluronidase comprising one or more amino acid substitutions relative to a wild-type hyaluronidase selected from the group consisting of HuPH20, HYAL1, HYAL2, HYAL3, HYAL4, HYALPS1, or a fragment thereof. In some embodiments, the endoglycosidase hydrolase enzyme comprises a modified hyaluronidase comprising one or more amino acid substitution in an alpha-helix region relative to a wild-type hyaluronidase selected from the group consisting of HuPH20, HYAL1, HYAL2, HYAL3, HYAL4, HYALPS1, or a fragment thereof. In some embodiments, the endoglycosidase hydrolase enzyme comprises a modified hyaluronidase

comprising one or more amino acid substitution in linker region relative to a wild-type hyaluronidase selected from the group consisting of HuPH20, HYAL1, HYAL2, HYAL3, HYAL4, HYALPS1, or a fragment thereof. In some embodiments, the endoglycosidase hydrolase enzyme comprises a modified hyaluronidase, wherein one or more N-terminal and/or C-terminal amino acids are deleted relative to a wild-type hyaluronidase selected from the group consisting of HuPH20, HYAL1, HYAL2, HYAL3, HYAL4, HYALPS1, or a fragment thereof. In some embodiments, the endoglycosidase hydrolase enzyme comprises a modified rHuPH20, wherein the modified rHuPH20 comprises: i. one or more amino acid substitution in an alpha-helix region, a linker region, or both an alpha- helix region and a linker region relative to wild-type rHuPH20; ii. deletion of one or more N- terminal amino acid, one or more C-terminal amino acid, or one or more N-terminal amino acid and one or more C-terminal amino acid relative to wild-type rHuPH20; or iii. both (i) and (ii).

**[00167]** "Hyaluronidase," as used herein, refers to an enzyme capable of catalyzing the cleavage of hyaluronan. Hyaluronan is a repeating polymer of N-acetyl-glucosamine and glucuronic acid, which is present in the subcutaneous space and contributes to the soluble gel-like component of the extracellular matrix of the skin and is restored by rapid turnover (resynthesis). In some embodiments, the hyaluronidase comprises rHuPH20, which is a glycosylated 447-amino acid single chain polypeptide that depolymerizes hyaluronan in the subcutaneous space locally at the site of injection in the skin. Depolymerization of hyaluronan by hyaluronidase is accomplished by hydrolysis of the polysaccharide polymer. Depolymerization of hyaluronan results in a transient reduction in the viscosity of the gel-like phase of the extracellular matrix and increased hydraulic conductance that facilitates the dispersion and absorption of the coadministered therapeutic agent. Thus, a hyaluronidase, *e.g.*, rHuPH20, can improve the speed and ease of subcutaneous delivery of injectable biologics and drugs by acting as a permeation enhancer. In certain embodiments, the hyaluronidase comprises ENHANZE™.

**[00168]** In any of the above embodiments, the pharmaceutical formulation may be a unit dosage form.

**[00169]** In an embodiment, the unit dosage form comprises the FcRn antagonist as a dry formulation for dissolution such as a lyophilized powder, freeze-dried powder, or water-free concentrate. In an embodiment, the dry formulation is comprised in a hermetically sealed container such as a vial, an ampoule, or a sachet.

**[00170]** In an embodiment, the unit dosage form comprises the FcRn antagonist as a liquid formulation, (*e.g.*, injection or infusion solution). In an embodiment, the liquid formulation is comprised in a hermetically sealed container such as a vial, a sachet, a pre-filled syringe, a pre-filled autoinjector, or a cartridge for a reusable syringe or applicator.

**[00171]** In an embodiment, the unit dosage per vial may contain 0.5 ml, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml, 10 ml, 15 ml, or 20 ml of an FcRn antagonist ranging from about 500 to about 2500 mg or from about 1000 mg to about 2000 mg. In an embodiment, these preparations can be adjusted to a desired concentration by adding a sterile diluent to each vial.

**[00172]** The formulations disclosed herein include bulk drug compositions useful in the manufacture of pharmaceutical compositions (*e.g.*, compositions that are suitable for administration to a subject or patient) which can be used in the preparation of unit dosage forms. In an embodiment, a composition of the invention is a pharmaceutical composition. Such compositions comprise a prophylactically or therapeutically effective amount of one or more prophylactic or therapeutic agents (*e.g.*, an FcRn antagonist of the invention or other prophylactic or therapeutic agent), and a pharmaceutically acceptable carrier. In an embodiment, the pharmaceutical compositions are formulated to be suitable for subcutaneous administration to a subject.

**Methods**

**[00173]** In an aspect, methods for treating pSS using an FcRn antagonist are provided. In certain embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof. An important goal and feature of the methods disclosed herein is improvement in one or more symptoms in pSS patients. Symptoms in pSS patients include, but are not limited to, dryness of mouth and eyes, dryness of nose, sinuses, ears, throat, skin, vagina, and/or prostate, fatigue, and musculoskeletal pain.

**[00174]** pSS can also affect the joints, muscles, nervous system (central nervous system and peripheral nervous system, including the autonomic nervous system), gastrointestinal tract (including the pancreas and liver), skin, blood vessels, lungs, and kidneys. Joint pain and stiffness with mild swelling is common, even in those without rheumatoid arthritis. Rashes may occur, including inflammation of small blood vessels (vasculitis), most commonly on the lower legs. Sun-sensitive rash is more common on the back, chest, face, and arms. Peripheral neuropathy can cause

numbness and tingling, especially in the feet, and can frequently pre-date symptoms of dryness. Fatigue, cognitive dysfunction, and sleep abnormalities are frequently reported symptoms.

**[00175]** Other symptoms in pSS patients include cutaneous lesions (*e.g.*, cutaneous vasculitis, annular erythema), pulmonary disorders (*e.g.*, large and/or small airway disease, bronchial/bronchiolar disease), vascular disorders (*e.g.*, Reynaud's phenomenon), renal disease (*e.g.*, glomerulonephritis, tubulointerstitial nephritis, cryoglobulinemia, proteinuria), neurological disorders (*e.g.*, pure sensory neuropathy), autonomic symptoms (*e.g.*, orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor symptoms), and/or hematological abnormalities (*e.g.*, cytopenia, raised erythrocyte sedimentation rate, anemia, leucopenia, thrombocytopenia, hypergammaglobulinemia).

**[00176]** Lymphadenopathy, fever, and lymphoma are also complications commonly observed in pSS patients.

**[00177]** Other goals and features of the methods disclosed herein include, but are not limited to, reduced dryness, reduced fatigue, reduced pain, improvement in tear gland function, improvement in salivary gland function, and improvement in disease-related quality of life. Effective treatment of pSS using an FcRn antagonist may include at least one of the elements of the group consisting of: improvement in one or more of the following: Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS), EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), clinical ESSDAI (clinESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), Sjögren's Tool for Assessing Response (STAR), Stimulated Whole Salivary Flow (SWSF), Unstimulated Whole Salivary Flow (UWSF), Salivary Gland Ultrasonography (SGUS), Schirmer's Test, Ocular Staining Score (OSS), Hocevar score.

**[00178]** Effective treatment of pSS using an FcRn antagonist may include change in the relative counts of lymphocytic infiltrate (optionally stained for CD45) in the parotid gland and/or change in B/B+T cell ratio in the parotid gland.

**[00179]** Effective treatment may also include at least one of the elements of the group consisting of: reduction in serum IgG, reduction in serum anti-Ro52/SS-A, reduction in serum anti-Ro60/SS-A, reduction in serum anti-La/SS-B, reduction in serum rheumatoid factor (RF), and reduction in serum C1q immune complexes.

**[00180]** The CRESS composite measures systemic disease activity, patient-reported symptoms, tear gland function, salivary gland function, and serology, developed to assess treatment efficacy in participants with pSS. Use of CRESS to assess pSS disease activity can be

advantageous over other measures that report on a single aspect of this heterogeneous disease. CRESS consists of the following items, with definitions of treatment response and lower disease activity:

- Systemic disease activity: as measured with clinESSDAI (see below). Response is defined as a score of <5 points.
- Patient-reported symptoms: as measured with ESSPRI (see below). Response is defined as a decrease of ≥1 point or ≥15% from baseline.
- Tear gland function: as measured with Schirmer's test and OSS (see below). If Schirmer's test is ≤5 mm at baseline (abnormal), a response is defined as an increase of at least 5 mm from baseline, or if OSS is ≥3 points at baseline (abnormal), a response is defined as a decrease of at least 2 points from baseline, or if both OSS and Schirmer's scores are normal at baseline, a response is defined as no change that results in an abnormal OSS or Schirmer's score.
- Salivary gland function: as measured with UWSF and SGUS (see below). A response is defined as at least 25% increase in UWSF score, or if UWSF score is 0 mL/min at baseline, any increase from baseline, or at least 25% decrease from baseline in total Hocevar score measured using SGUS.
- Serology: as measured with serum IgG and RF. A response is defined as a decrease in serum RF of at least 25% from baseline, or a decrease in serum IgG of at least 10% from baseline.

**[00181]** The ESSDAI measures disease activity in patients with pSS. The ESSDAI consists of 12 domains, 11 related to organ involvement (cutaneous, pulmonary, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, and lymphadenopathic) and 1 biological domain reflecting B-cell activity. The activity levels of each domain (range: 0-3 points) are multiplied by their respective weights (range: 1-6 points) to obtain the total score. (See **Table S4**). Total score ranges from 0-123 points. A score of <5 indicates low disease activity; a score of 5-13 indicates moderate disease activity; a score of ≥14 indicates high disease activity.

**[00182]** ClinESSDAI derives from the ESSDAI, and its score provides an accurate evaluation of disease activity independent of B-cell biomarkers. The clinical domains in clinESSDAI have different weights than in ESSDAI (See **Table S5**). Total score ranges from 0-

135 points. A score of <5 indicates low disease activity; a score of 5-13 indicates moderate disease activity; a score of ≥14 indicates high disease activity.

**[00183]** STAR assesses the efficacy of treatments for pSS. A response is defined as a STAR score of ≥5. This composite measure contains 5 domains:

- Systemic activity (3 points): clinESSDAI decrease of ≥3 points;
- Patient-reported outcome (3 points): ESSPRI decrease of at least 1 point or ≥15%;
- Lacrimal gland function (1 point; assessed by Schirmer's test or OSS): Schirmer's test - if abnormal score at baseline: increase of ≥5 mm from baseline; if normal score at baseline: no change to abnormal; OSS - if abnormal score at baseline: decrease of ≥2 points from baseline; if normal score at baseline: no change to abnormal;
- Salivary gland function (1 point): UWSF - if score >0 at baseline: increase of ≥25% from baseline; if score is 0 at baseline: any increase in UWSF from baseline; or SGUS - ≥25% decrease in total Hocevar score from baseline;
- Biological (1 point; assessed by IgG or RF): IgG: ≥10% reduction or RF: ≥25% decrease.

**[00184]** ESSPRI is a questionnaire that measures self-reported symptoms in participants with pSS. The ESSPRI has 3 items that measure dryness, fatigue, and pain over a recall period of "the last 2 weeks." Each item includes a numeric rating scale ranging from 0 "No symptoms (dryness, fatigue, or pain)" to 10 "Maximal imaginable (dryness, fatigue, or pain)." The total global score ranges from 0 to 10 and the ESSPRI is calculated by averaging the numeric scores for pain, fatigue, and dryness, with higher scores indicating more symptoms. It has been validated in participants with pSS.

**[00185]** PGA is a tool that measures a participant's global evaluation of their overall disease activity at the time of assessment. The participant rates their overall disease activity by drawing a vertical mark on a 10-cm VAS from the left end of the line (no evidence of disease activity) to the right end of the line (extremely active or severe disease activity).

**[00186]** The SGUS Hocevar grading system rates 5 parameters: parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hypoechogenic reflections, and the clearness of salivary gland borders. The overall ultrasound score is calculated by summation of the grades for

the 5 subscores for all 4 major salivary glands. The overall ultrasound score can range from 0 to 48.

**[00187]** Schirmer's test is an assessment of tear gland function in which a strip of filter paper is applied under the eyelid to measure the quantity of tear production. A result of ≤5 mm indicates abnormal tear gland function.

**[00188]** OSS is another assessment of tear gland function. OSS uses lissamine green dye to grade the conjunctiva and fluorescent dye to grade the cornea. A score of ≥3 points indicates abnormal tear gland function.

**[00189]** In some embodiments, the pSS may be characterized as meeting ACR/EULAR criteria. In some embodiments, the pSS may be characterized as meeting ACR/EULAR 2016 criteria. In some embodiments, the pSS may be characterized as meeting ACR/EULAR criteria ≤7 years before administration of an FcRn antagonist. In some embodiments, the pSS may be characterized as meeting ACR/EULAR 2016 criteria ≤7 years before administration of an FcRn antagonist.

**[00190]** In some embodiments, the pSS may be characterized by one or more of the following symptoms in a subject: daily, persistent, troublesome dry eyes for more than 3 months; recurrent sensation of sand or gravel in the eyes; use of tear substitutes more than 3 times a day; daily feeling of dry mouth for more than 3 months; and/or frequently drinking liquids to aid in swallowing dry food.

**[00191]** In some embodiments, the pSS may be characterized by an ESSDAI of ≥5 in a subject. In some embodiments, the pSS may be characterized by at least one positive domain item from the ESSDAI questionnaire in a subject.

**[00192]** In some embodiments, the pSS may be characterized by one or more of the following symptoms in a subject: labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1; anti-Ro/SS-A positive; OSS of ≥5 (or van Bijsterfeld score of ≥4) on at least one eye; Schirmer's test of ≤5mm/5 minutes on at least one eye; and/or UWSF rate of ≤0.1 mL/min.

**[00193]** In some embodiments, the pSS may be characterized by a score of ≥4 when summing the weights of the items presented in **Table S1**.

**[00194]** In some embodiments, the pSS may be characterized by presence of autoantibodies in a subject. In some embodiments, the autoantibody may be one or more of an anti-Ro/SS-A autoantibody, an anti-La/SS-B autoantibody, an ANA autoantibody, or rheumatoid factor (RF). In

some embodiments, the pSS may be characterized by presence of anti-Ro/SS-A autoantibodies in a subject. In some embodiments, the presence of autoantibodies is detected in serum from the subject.

**[00195]** In some embodiments, the pSS may be characterized by residual salivary flow in a subject. In some embodiments, the pSS may be characterized by a UWSF rate of >0 in a subject. In some embodiments, the pSS may be characterized by a SWSF rate >0.10 in a subject. In some embodiments, the pSS may be characterized by a UWSF rate of >0 and a SWSF rate of >0.10 in a subject.

**[00196]** In some embodiments, the pSS may be characterized by serum total IgG ≥6 g/L in a subject. In some embodiments, the pSS may be characterized by serum total IgG ≥4 g/L in a subject.

**[00197]** In some embodiments, the subject has at least a moderate level of systemic disease activity.

**[00198]** In some embodiments, the subject has not been diagnosed with, or received treatment for, one or more of the following conditions: AIDS, active hepatitis C infection, sarcoidosis, amyloidosis, graft-versus-host disease, history of head and neck radiation treatment, or IgG4-related disease. In some embodiments, the subject has not been diagnosed with, or received treatment for, any of the following conditions: AIDS, active hepatitis C infection, sarcoidosis, amyloidosis, graft-versus-host disease, history of head and neck radiation treatment, or IgG4-related disease.

**[00199]** In some embodiments, the subject has not been diagnosed with, or received treatment for, a secondary SS overlap syndrome where another confirmed autoimmune rheumatic or systemic inflammatory condition is the primary diagnosis. In some embodiments, the subject has not received a primary diagnosis of one or more of the following conditions: rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or inflammatory bowel disease. In some embodiments, the subject has not received a primary diagnosis of any of the following conditions: rheumatoid arthritis, systemic lupus erythematosus, scleroderma, or inflammatory bowel disease.

**[00200]** In some embodiments, the subject has no history of malignancy unless considered cured by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of IMP. In some embodiments, subjects do have basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, carcinoma in situ of the breast, or incidental histological finding of prostate cancer (TNM stage T1a or T1b).

**[00201]** In some embodiments, the subject does not have significant uncontrolled active or chronic bacterial, viral, or fungal infection, or positive SARS-CoV-2 PCR test. In some embodiments, the subject has no positive serum test for hepatitis B virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HB surface antigen (HBsAg) or negative HBV DNA test, hepatitis C virus (HCV) based on HCV antibody assay unless a negative RNA test is available, or HIV. In some embodiments, the subject does not have total IgG <4 g/L.

**[00202]** In some embodiments, the subject has not been treated with a biologic disease-modifying antirheumatic drug (DMARD) prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with a biologic DMARD within 24 weeks prior to administration of an FcRn antagonist.

**[00203]** In some embodiments, the subject has not been treated with one or more of the following: intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), or plasma exchange (PLEX) prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with any of the following: IVIg, SCIg, or PLEX prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with one or more of the following: IVIg, SCIg, or PLEX within 12 weeks prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with any of the following: IVIg, SCIg, or PLEX within 12 weeks prior to administration of an FcRn antagonist.

**[00204]** In some embodiments, the subject has not been treated with one or more of the following: a pharmacological stimulant for salivary or lacrimal glands, pilocarpine, systemic corticosteroids, antimalarials, conventional DMARDs, or JAK inhibitors prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with any of the following: a pharmacological stimulant for salivary or lacrimal glands, pilocarpine, systemic corticosteroids, antimalarials, conventional DMARDs, or JAK inhibitors prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with one or more of the following: a pharmacological stimulant for salivary or lacrimal glands, pilocarpine, systemic corticosteroids, antimalarials, conventional DMARDs, or JAK inhibitors within 4 weeks prior to administration of an FcRn antagonist. In some embodiments, the subject has not been treated with any of the following: a pharmacological stimulant for salivary or lacrimal glands, pilocarpine, systemic corticosteroids, antimalarials, conventional DMARDs, or JAK inhibitors within 4 weeks prior to administration of an FcRn antagonist.

**[00205]** In some embodiments, the FcRn antagonist is administered at a fixed dose of about 20 mg to about 20,000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of about 200 mg to about 20,000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of about 300 mg to about 6000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of about 750 mg to about 3000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of about 1000 mg to about 2500 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of about 1000 mg to about 2000 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00206]** In some embodiments, the FcRn antagonist is administered at a fixed dose of 20 mg to 20,000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of 200 mg to 20,000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of 300 mg to 6000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of 750 mg to 3000 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of 1000 mg to 2500 mg. In some embodiments, the FcRn antagonist is administered at a fixed dose of 1000 mg to 2000 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00207]** In some embodiments, the FcRn antagonist is administered at a fixed dose of about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 500 mg, about 750 mg, about 1000 mg, about 1500 mg, about 2000 mg, about 2500 mg, about 3000 mg, about 4000 mg, about 5000 mg, about 6000 mg, about 7000 mg, about 8000 mg, about 9000 mg, about 10,000 mg, about 11,000 mg, about 12,000 mg, about 13,000 mg, about 14,000 mg, about 15,000 mg, about 16,000 mg, about 17,000 mg, about 18,000 mg, about 19,000 mg, or about 20,000 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00208]** In some embodiments, the FcRn antagonist is administered at a fixed dose of 20 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, 2000 mg, 2500 mg, 3000 mg, 4000 mg, 5000 mg, 6000 mg, 7000 mg, 8000 mg, 9000 mg, 10,000 mg, 11,000 mg, 12,000 mg, 13,000 mg, 14,000 mg, 15,000 mg, 16,000 mg, 17,000 mg, 18,000 mg, 19,000 mg, or 20,000 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00209]** In some embodiments, the FcRn antagonist is administered at a dose of about 0.2 mg/kg to about 200 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of about 2 mg/kg to about 200 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of about 2 mg/kg to about 120 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of about 3 mg/kg to about 60 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of about 10 mg/kg to about 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00210]** In some embodiments, the FcRn antagonist is administered at a dose of 0.2 mg/kg to 200 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of about 2 mg/kg to about 200 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of 2 mg/kg to 120 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of 3 mg/kg to 60 mg/kg. In some embodiments, the FcRn antagonist is administered at a dose of 10 mg/kg to 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00211]** In some embodiments, the FcRn antagonist is administered at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 15 mg/kg, about 17.5 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 110 mg/kg, about 120 mg/kg, about 130 mg/kg, about 140 mg/kg, about 150 mg/kg, about 160 mg/kg, about 170 mg/kg, about 180 mg/kg, about 190 mg/kg, or about 200 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00212]** In some embodiments, the FcRn antagonist is administered at a dose of 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 12.5 mg/kg, 15 mg/kg, 17.5 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, 100 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg, or 200 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00213]** In some embodiments, the FcRn antagonist is administered intravenously. In some embodiments, the FcRn antagonist is administered intravenously once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00214]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 0.2 mg/kg to about 200 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 2 mg/kg to about 200 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 2 mg/kg to about 120 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 3 mg/kg to about 60 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 10 mg/kg to about 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00215]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 0.2 mg/kg to 200 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 2 mg/kg to 200 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 2 mg/kg to 120 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 3 mg/kg to 60 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 10 mg/kg to 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00216]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 12.5 mg/kg, about 15 mg/kg, about 17.5 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 110 mg/kg, about 120 mg/kg, about 130 mg/kg, about 140 mg/kg, about 150 mg/kg,

about 160 mg/kg, about 170 mg/kg, about 180 mg/kg, about 190 mg/kg, or about 200 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00217]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 12.5 mg/kg, 15 mg/kg, 17.5 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg, 65 mg/kg, 70 mg/kg, 75 mg/kg, 80 mg/kg, 85 mg/kg, 90 mg/kg, 95 mg/kg, 100 mg/kg, 110 mg/kg, 120 mg/kg, 130 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 170 mg/kg, 180 mg/kg, 190 mg/kg, or 200 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00218]** In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 10 mg/kg to about 30 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 10 mg/kg to about 25 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 10 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 15 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 20 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 25 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of about 30 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 10 mg/kg to 30 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 10 mg/kg to 25 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 10 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 15 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 20 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose of 25 mg/kg. In some embodiments, the FcRn antagonist is administered intravenously once weekly or once every two weeks at a dose

of 30 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00219]** In some embodiments, the FcRn antagonist is administered intravenously once every two weeks for 52 weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00220]** In some embodiments, the FcRn antagonist is administered subcutaneously. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00221]** In some embodiments, FcRn antagonist is administered subcutaneously at a fixed dose of about 20 mg to about 20,000 mg. In some embodiments, FcRn antagonist is administered subcutaneously at a fixed dose of about 100 mg to about 10,000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 750 mg to 3000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 1000 mg to 2000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00222]** In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of about 20 mg, about 50 mg, about 100 mg, about 250 mg, about 500 mg, about 750 mg, about 1000 mg, about 1500 mg, about 2000 mg, about 3000 mg, about 4000 mg, about 5000 mg, about 6000 mg, about 7000 mg, about 8000 mg, about 9000 mg, about 10,000 mg, about 11,000 mg, about 12,000 mg, about 13,000 mg, about 14,000 mg, about 15,000 mg, about 16,000 mg, about 17,000 mg, about 18,000 mg, about 19,000 mg, or about 20,000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00223]** In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 20 mg, 50 mg, 100 mg, 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, 2000 mg, 3000 mg, 4000 mg, 5000 mg, 6000 mg, 7000 mg, 8000 mg, 9000 mg, 10,000 mg, 11,000 mg, 12,000 mg, 13,000 mg, 14,000 mg, 15,000 mg, 16,000 mg, 17,000 mg, 18,000 mg, 19,000 mg, or 20,000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once

monthly, or once every six weeks. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 1000 mg or 2000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00224]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly or every two weeks at a fixed dose of about 750 mg to about 3000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly or every two weeks at a fixed dose of about 1000 mg to about 2000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of about 1000 mg or about 2000 mg once weekly or every two weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00225]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly or every two weeks at a fixed dose of 750 mg to 3000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 750 mg to 3000 mg once weekly. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 750 mg to 3000 mg once every two weeks. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 750 mg to 3000 mg once every three weeks. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 750 mg to 3000 mg once monthly. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly or every two weeks at a fixed dose of 1000 mg to 2000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously at a fixed dose of 1000 mg or 2000 mg once weekly or every two weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00226]** In some embodiments, the FcRn antagonist is first administered subcutaneously at a fixed dose of about 1000 mg twice on the same day. In some embodiments, the FcRn antagonist is first administered subcutaneously at a fixed dose of 1000 mg twice on the same day. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00227]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 750 mg to about 1750 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 800 mg to about 1200 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 750 mg. In some embodiments, the FcRn antagonist is administered

subcutaneously once weekly at a fixed dose of about 800 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 1000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 1200 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 1250 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 1500 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of about 1750 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00228]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 750 mg to 1750 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 800 mg to 1200 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 750 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 800 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 1000 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 1200 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 1250 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 1500 mg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a fixed dose of 1750 mg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00229]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of about 10 mg/kg to about 25 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of about 10 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of about 15 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of about 20 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of about 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00230]** In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of 10 mg/kg to 25 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of 10 mg/kg. In some embodiments, the FcRn

antagonist is administered subcutaneously once weekly at a dose of 15 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of 20 mg/kg. In some embodiments, the FcRn antagonist is administered subcutaneously once weekly at a dose of 25 mg/kg. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00231]** In some embodiments, the FcRn antagonist is first administered intravenously and is subsequently administered subcutaneously. In some embodiments, the FcRn antagonist is first administered intravenously and is subsequently administered subcutaneously at fixed dose of 100 mg to 10,000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is first administered intravenously and is subsequently administered subcutaneously at fixed dose of 1000 mg or 2000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00232]** In some embodiments, one or more doses of the FcRn antagonist are administered intravenously and subsequent doses of the FcRn antagonist are administered subcutaneously. In some embodiments, one or more doses of the FcRn antagonist are administered intravenously and subsequent doses of the FcRn antagonist are administered subcutaneously at fixed dose of 100 mg to 10,000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, one or more doses of the FcRn antagonist are administered intravenously and subsequent doses of the FcRn antagonist are administered subcutaneously at fixed dose of 1000 mg or 2000 mg once weekly, once every two weeks, once every three weeks, once every four weeks, once monthly, or once every six weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00233]** In some embodiments, the FcRn antagonist is administered for 6, 12, 24, 39, or 52 weeks or less. In some embodiments, the FcRn antagonist is administered for 24 weeks or less. In some embodiments, the FcRn antagonist is administered for 52 weeks or less. In some embodiments, the FcRn antagonist is administered for at least 6, 12, 24, 39, or 52 weeks. In some embodiments, the FcRn antagonist is administered for at least 24 weeks. In some embodiments, the FcRn antagonist is administered for 24 weeks. In some embodiments, the FcRn antagonist is administered for at least 52 weeks. In some embodiments, the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

**[00234]** In some embodiments, the method further comprises administering to the subject an additional therapeutic compound.

**[00235]** In some embodiments, the method further comprises administering to the subject an effective amount of an anticholinergic agent.

**[00236]** In some embodiments, the method further comprises administering to the subject a topical medication. In some embodiments, the method further comprises administering to the subject an effective amount of one or more of the following: an ophthalmic lubricant, an ophthalmic lubricating ointment, a hydroxyl cellulose insert, or a saliva substitute. In some embodiments, the method further comprises administering to the subject an effective amount of a pharmacological stimulant for salivary and/or lacrimal glands. In some embodiments, the method further comprises administering to the subject an effective amount of one or more of the following: cyclosporine, lifitegrast, pilocarpine, or cevimeline.

**[00237]** In some embodiments, the method further comprises administering to the subject an effective amount of one or more of the following: a DMARD, a janus kinase (JAK) inhibitor, an NSAID (*e.g.*, ibuprofen, naproxen), acetaminophen, or an antimalarial (*e.g.*, hydroxychloroquine).

**[00238]** In some embodiments, the method further comprises administering to the subject an effective amount of a DMARD. Examples of DMARDs include, but are not limited to, hydroxychloroquine, chloroquine phosphate, methotrexate, azathioprine, and mycophenolate mofetil.

**[00239]** In an embodiment, the method further comprises administering to the subject an effective amount of a corticosteroid and/or an immunosuppressive agent. In an embodiment, the method further comprises administering to the subject an effective amount of a corticosteroid. In an embodiment, method further comprises administering to the subject an effective amount of a glucocorticoid. In an embodiment, the method further comprises administering to the subject an effective amount of a glucocorticoid intravenously and/or administering to the subject an effective amount of a glucocorticoid orally. In an embodiment, the method further comprises administering to the subject an effective amount of a glucocorticoid intravenously and administering to the subject an effective amount of a glucocorticoid orally.

**[00240]** In an embodiment, the method further comprises administering to the subject an oral corticosteroid at a dose of $\leq$10 mg/day.

**[00241]** In an embodiment, the method further comprises administering to the subject an effective amount of prednisone. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 7.5 mg/day to 75 mg/day, to a maximum of 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 8 mg/day to 72 mg/day, to a maximum of 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 9 mg/day to 66 mg/day, to a maximum of 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 10 mg/day to 60 mg/day, to a maximum of 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 0.5 mg/kg/day to 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 0.6 mg/kg/day to 1 mg/kg/day. In an embodiment, the method further comprises administering to the subject prednisone at a dose of 0.6 mg/kg/day to 1 mg/kg/day, to a maximum of 80 mg/day. In an embodiment, the prednisone is administered orally.

**[00242]** In an embodiment, the method further comprises administering to the subject an effective amount of methylprednisolone. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 100 mg to 1250 mg, for up to three days. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 150 mg to 1200 mg, for up to three days. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 200 mg to 1100 mg, for up to three days. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 500 mg to 1000 mg, for up to three days. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 0.25 g/day to 0.5 g/day. In an embodiment, the method further comprises administering to the subject methylprednisolone at a dose of 0.25 g/day to 0.5 g/day, for one to three days. In an embodiment, the methylprednisolone is administered intravenously.

**[00243]** In an embodiment, the method further comprises administering to the subject an effective amount of prednisone orally and an effective amount of methylprednisolone intravenously. In an embodiment, the method further comprises administering to the subject prednisone orally at a dose of 10 mg/day to 60 mg/day, to a maximum of 1 mg/kg/day, and methylprednisolone intravenously at a dose of 500 mg to 1000 mg, for up to three days. In an embodiment, the method further comprises administering to the subject prednisone orally at a dose of 0.5 mg/kg/day to 1 mg/kg/day, and methylprednisolone intravenously at a dose of 500 mg to

1000 mg, for up to three days. In an embodiment, the method further comprises administering to the subject prednisone orally at a dose of 0.6 mg/kg/day to 1 mg/kg/day, to a maximum of 80 mg/day, and methylprednisolone intravenously at a dose of 0.25 g/day to 0.5 g/day, for one to three days.

**[00244]** In an embodiment, the method further comprised administering to the subject an effective amount of an immunosuppressive agent. Examples of immunosuppressive agents include, without limitation, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, and cyclophosphamide.

**[00245]** In an embodiment, the method further comprises administering to the subject an effective amount of a B-lymphocyte targeting biologic. Examples of B-lymphocyte targeting biologics include, without limitation, belimumab, rituximab, and obinutuzumab. In an embodiment, the method further comprises administering to the subject an effective amount of belimumab. In an embodiment, the method further comprises administering to the subject belimumab intravenously at a dose of 10 mg/kg once every two weeks for three doses, then once every four weeks for subsequent doses. In an embodiment, the method further comprises administering to the subject belimumab intravenously at a dose of 10 mg/kg once every two weeks for three doses, then once every four weeks for subsequent doses, and a mycophenolic acid analog. In an embodiment, the method further comprises administering to the subject belimumab intravenously at a dose of 10 mg/kg once every two weeks for three doses, then once every four weeks for subsequent doses, and cyclophosphamide. In an embodiment, the method further comprises administering to the subject belimumab intravenously at a dose of 10 mg/kg once every two weeks for three doses, then once every four weeks for subsequent doses, and cyclophosphamide at a dose of 500 mg once every two weeks for six months. In an embodiment, the method further comprises administering to the subject an effective amount of rituximab. In an embodiment, the method further comprises administering to the subject rituximab at a dose of 1 g on days 1 and 15 as add-on therapy for refractory cases or for corticosteroid minimization. In an embodiment, the method further comprises administering to the subject an effective amount of obinutuzumab.

**[00246]** In an embodiment, when the subject is administered the FcRn antagonist, the dose of prednisone is tapered over 12 weeks to a dose of 7.5 mg/day. In an embodiment, the initial oral prednisone dose is at 0.5 mg/kg/day to 1 mg/kg/day, not to exceed 60 mg/day.

**[00247]** In some embodiments, treatment of pSS is characterized by the subject exhibiting one or more responses (*e.g.*, clinically established results) following administration of the FcRn antagonist. In some embodiments, treatment of pSS is characterized by the subject exhibiting two or more responses following administration of the FcRn antagonist. In some embodiments, treatment of pSS is characterized by the subject exhibiting three or more responses following administration of the FcRn antagonist. In some embodiments, treatment of pSS is characterized by the subject exhibiting four or more responses following administration of the FcRn antagonist. In some embodiments, treatment of pSS is characterized by the subject exhibiting five responses following administration of the FcRn antagonist. In some embodiments, the responses are selected from the group consisting of: 1) a clinical ESSDAI (clinESSDAI) score of <5 points; 2) a decrease in EULAR Sjögren's syndrome patient reported index (ESSPRI) score of ≥1 point or ≥15%, compared to a baseline value; 3) an increase in tear gland function; 4) an increase in salivary gland function; and 5) a decrease in serum rheumatoid factor (RF) of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value. In some embodiments, the baseline value of any of the above is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value of any of the above is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, one or more of the responses are measured 16 weeks and/or 24 weeks after administration of an FcRn antagonist. In some embodiments, one or more of the responses are measured 16 weeks and/or 24 weeks after an initial administration of the FcRn antagonist. In some embodiments, one or more of the responses are measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, one or more of the responses are measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00248]** In some embodiments, the subject shows all of the following responses: 1) a clinESSDAI score of <5 points; 2) an increase in tear gland function; 3) an increase in salivary gland function; and 4) a decrease in serum rheumatoid factor (RF) of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value, following administration of the FcRn antagonist. In some embodiments, the baseline value of any of the above is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value of any of the above is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, the responses are measured 16 weeks and/or 24 weeks after administration of an FcRn antagonist. In some embodiments, the

responses are measured 16 weeks and/or 24 weeks after an initial administration of the FcRn antagonist. In some embodiments, the responses are measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, the responses are measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00249]** In some embodiments, the increase in tear gland function is measured by Schirmer's test and/or ocular staining score (OSS). In some embodiments, if the subject shows a baseline value of ≤5 mm as measured by Schirmer's test, a tear gland response is defined as an increase of at least 5 mm from the baseline value. In some embodiments, if the subject shows a baseline value of ≥3 points as measured by OSS, a tear gland response is defined as a decrease of at least 2 points from the baseline value. In some embodiments, if the subject shows a baseline value of > 5 mm as measured by Schirmer's test and shows a baseline value of < 3 points as measured by OSS, a tear gland response is defined as no change that results in an abnormal OSS or Schirmer's score. In some embodiments, the baseline value of any of the above is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value of any of the above is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, tear gland response is measured 16 weeks and/or 24 weeks after administration of the FcRn antagonist. In some embodiments, tear gland response is measured 16 weeks and/or 24 weeks after an initial administration of the FcRn antagonist. In some embodiments, tear gland response is measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, tear gland response is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00250]** In some embodiments, the increase in salivary gland function is measured by UWSF and/or salivary gland ultrasonography (SGUS). In some embodiments, a salivary gland response is defined as an increase in UWSF in the subject of at least 25%, compared to a baseline value if the baseline value is > 0 mL/min, or any increase in UWSF in the subject if the baseline value is 0 mL/min. In some embodiments, a salivary gland response is defined as a decrease in Hocevar score in the subject as measured by SGUS of at least 25%, compared to a baseline value. In some embodiments, the baseline value of any of the above is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value of any of the above is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, salivary gland response is measured 16 weeks and/or 24 weeks after administration of the FcRn antagonist. In some embodiments, salivary gland response is measured 16 weeks

and/or 24 weeks after an initial administration of the FcRn antagonist. In some embodiments, salivary gland response is measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, salivary gland response is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00251]** In some embodiments, the subject shows a decrease in ESSDAI score and/or clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the baseline value is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured 16 weeks and/or 24 weeks following administration of the FcRn antagonist. In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured 16 weeks and/or 24 weeks following an initial administration of the FcRn antagonist. In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, the ESSDAI score and/or the clinESSDAI score is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00252]** In some embodiments, the subject shows a decrease of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 points in the ESSDAI score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 points in the clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of at least 3 points in the ESSDAI score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of at least 4 points in the clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of at least 5 points in the clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value.

**[00253]** In some embodiments, the subject achieves low disease activity (ClinESSDAI score $< 5$) following administration of the FcRn antagonist. In some embodiments, the subject achieves low disease activity (ClinESSDAI score $< 5$) following administration of the FcRn antagonist for 16 weeks. In some embodiments, the subject achieves low disease activity (ClinESSDAI score $< 5$) following administration of the FcRn antagonist once weekly for 16

weeks. In some embodiments, the subject achieves low disease activity (ClinESSDAI score < 5) following administration of the FcRn antagonist for 24 weeks. In some embodiments, the subject achieves low disease activity (ClinESSDAI score < 5) following administration of the FcRn antagonist once weekly for 24 weeks.

**[00254]** In some embodiments, the subject shows an increase in Sjögren's Tool for Assessing Response (STAR) score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the baseline value is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, the STAR score is measured 24 weeks following administration of the FcRn antagonist. In some embodiments, the STAR score is measured 24 weeks following an initial administration of the FcRn antagonist. In some embodiments, the STAR score is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00255]** In some embodiments, the subject has a STAR score of ≥1, ≥2, ≥3, ≥4, ≥5, ≥6, ≥7, or ≥8 following administration of the FcRn antagonist. In some embodiments, the subject has a STAR score of ≥5 following administration of the FcRn antagonist. In some embodiments, the STAR score is measured 24 weeks following administration of the FcRn antagonist. In some embodiments, the STAR score is measured 24 weeks following an initial administration of an initial dose of the FcRn antagonist. In some embodiments, the STAR score is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00256]** In some embodiments, the subject shows an improvement in total Multidimensional Fatigue Inventory (MFI) score, SF-36 physical component score, SF-36 mental component score, PGA score, EQ-5D-5L score, VAS score, ESSPRI dryness score, ESSPRI fatigue score, ESSPRI pain score, and/or PASS score, following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the baseline value is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, the total MFI score, the SF-36 physical component score, the SF-36 mental component score, the PGA score, the EQ-5D-5L score, the VAS score, the ESSPRI dryness score, the ESSPRI fatigue score, the ESSPRI pain score, and/or the PASS score is measured at 16 weeks and/or 24 weeks following administration of the FcRn antagonist. In some embodiments, the total MFI score, the SF-36 physical component score, the SF-36 mental component score, the PGA score, the EQ-5D-5L

score, the VAS score, the ESSPRI dryness score, the ESSPRI fatigue score, the ESSPRI pain score, and/or the PASS score is measured at 16 weeks and/or 24 weeks following an initial administration of the FcRn antagonist. In some embodiments, the total MFI score, the SF-36 physical component score, the SF-36 mental component score, the PGA score, the EQ-5D-5L score, the VAS score, the ESSPRI dryness score, the ESSPRI fatigue score, the ESSPRI pain score, and/or the PASS score is measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, the total MFI score, the SF-36 physical component score, the SF-36 mental component score, the PGA score, the EQ-5D-5L score, the VAS score, the ESSPRI dryness score, the ESSPRI fatigue score, the ESSPRI pain score, and/or the PASS score is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00257]** In some embodiments, the subject shows a change in SWSF rate, UWSF rate, Hocevar score, Schirmer's test score, and/or OSS, following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the baseline value is obtained from the subject prior to administration of the FcRn antagonist. In some embodiments, the baseline value is obtained from the subject prior to an initial administration of the FcRn antagonist. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured at 16 weeks and/or 24 weeks following administration of the FcRn antagonist. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured at 16 weeks and/or 24 weeks following an initial administration of the FcRn antagonist. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured after administration of the FcRn antagonist once weekly for 16 weeks. In some embodiments, the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured after administration of the FcRn antagonist once weekly for 24 weeks.

**[00258]** In some embodiments, the subject shows an increase in SWSF rate following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows an increase in SWSF rate of 0.05 to 0.5 mL/min following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows an increase in SWSF rate of 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, or 0.5 mL/min following administration of the FcRn antagonist, compared to a baseline value.

**[00259]** In some embodiments, the subject shows an increase in UWSF rate following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the

baseline value is 0 mL/min. In some embodiments, the baseline value is ≤0.1 mL/min. In some embodiments, the UWSF rate following administration of the FcRn antagonist is about 0.3-0.4 mL/min. In some embodiments, the subject shows an increase in UWSF rate of 0.05 to 0.3 mL/min following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows an increase in USWF rate of 0.05, 0.1, 0.15, 0.2, 0.25, or 0.3 mL/min following administration of the FcRn antagonist. In some embodiments, the subject shows at least a 25% increase in UWSF rate following administration of the FcRn antagonist, compared to a baseline value.

**[00260]** In some embodiments, the subject shows a decrease in Hocevar score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of 0.5 to 9 in Hocevar score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, or 9 in Hocevar score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows at least a 25% decrease in Hocevar score following administration of the FcRn antagonist, compared to a baseline value.

**[00261]** In some embodiments, the subject shows an increase in Schirmer's test score following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows an increase in Schirmer's test score of ≥5 mm/5 minutes in one or both eyes following administration of the FcRn antagonist if the baseline value is abnormal (≤5 mm/5 minutes in one or both eyes). In some embodiments, the subject shows an increase in Schirmer's test score of 0.5 to 15 mm/5 min in one or both eyes. In some embodiments, the subject shows an increase in Schirmer's test score of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 mm/5 min in one or both eyes.

**[00262]** In some embodiments, the subject shows a decrease in OSS following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a decrease in OSS of 0.1 to 5 points after administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows a 0.1-point decrease, a 0.5-point decrease, a 1-point decrease, a 1.5-point decrease, a 2-point decrease, a 2.5-point decrease, a 3-point decrease, a 3.5-point decrease, a 4-point decrease, a 4.5-point decrease, or a 5-point decrease in OSS in one or both eyes following administration of the FcRn antagonist, compared to a baseline value. In some embodiments, the subject shows at least a 2-point decrease in OSS in one or both eyes following administration of the FcRn antagonist, compared to a baseline value.

In some embodiments, the subject shows at least a 2-point decrease in OSS in one or both eyes following administration of the FcRn antagonist if the baseline value is abnormal ($\geq$ 3 points).

**[00263]** In some embodiments, after administering the FcRn antagonist to the subject, the subject exhibits a post-administration level of a serum autoantibody that is reduced as compared to a baseline level of the serum autoantibody obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the post-administration level of the serum autoantibody is reduced by at least 5%, at least 10%, at least 15%, or at least 20%, as compared to the baseline level of the serum autoantibody obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the post-administration level of the serum autoantibody is measured 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and/or 24 weeks after administering the FcRn antagonist to the subject. In some embodiments, the post-administration level of the serum autoantibody is measured 1 week, 2 weeks, 4 weeks, 12 weeks, 16 weeks, 20 weeks, and/or 24 weeks after an initial administration of the FcRn antagonist to the subject. In some embodiments, the serum autoantibody level is measured 4 weeks, 16 weeks, and/or 24 weeks following administration of the FcRn antagonist. In some embodiments, the serum autoantibody level is measured 4 weeks, 16 weeks, and/or 24 weeks following an initial administration of the FcRn antagonist. In some embodiments, the serum autoantibody level is measured following administration of the FcRn antagonist weekly for 4 weeks. In some embodiments, the serum autoantibody level is measured following administration of the FcRn antagonist weekly for 16 weeks. In some embodiments, the serum autoantibody level is measured following administration of the FcRn antagonist weekly for 24 weeks. Examples of autoantibodies associated with pSS include, but are not limited to, anti-Ro52/SS-A antibodies, anti-Ro60/SS-A antibodies, anti-La/SS-B antibodies, rheumatoid factor (RF), and antinuclear antibodies (ANA). In some embodiments, the autoantibody is an anti-Ro52/SS-A antibody, an anti-Ro60/SS-A antibody, or an anti-La/SS-B antibody. In some embodiments, the autoantibody is an anti-Ro52/SS-A antibody, an anti-Ro60/SS-A antibody, an anti-La/SS-B antibody, RF, an antinuclear antibody or any combination thereof. In some embodiments, the autoantibody is an IgA-related autoantibody, an IgM-related autoantibody, or an IgG-related autoantibody.

**[00264]** In some embodiments, after administering the FcRn antagonist to the subject, the subject exhibits a post-administration level of circulating immune complexes that is reduced as compared to a baseline level of circulating immune complexes obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the circulating immune complexes are

selected from the group consisting of C3, C4, CH50, and C1q-binding circulating immune complexes. In some embodiments, the post-administration level of circulating immune complexes is reduced by at least 10%, at least 25%, at least 50%, at least 75%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, as compared to the baseline level of circulating immune complexes obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the post-administration level of circulating immune complexes is measured 4 weeks, 16 weeks, and/or 24 weeks after administering the FcRn antagonist to the subject. In some embodiments, the post-administration level of circulating immune complexes is measured 4 weeks, 16 weeks, and/or 24 weeks after an initial administration of the FcRn antagonist to the subject.

**[00265]** In some embodiments, after administering the FcRn antagonist to the subject, the subject exhibits a post-administration level of serum IgG that is reduced as compared to a baseline level of serum IgG obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the post-administration level of serum IgG is reduced by at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, or at least 65%, as compared to the baseline level of serum IgG obtained from the subject prior to administering the FcRn antagonist. In some embodiments, the post-administration level of serum IgG is measured 4 weeks, 16 weeks, and/or 24 weeks after administering the FcRn antagonist to the subject. In some embodiments, the post-administration level of serum IgG is measured 4 weeks, 16 weeks, and/or 24 weeks after an initial administration of the FcRn antagonist to the subject. In some embodiments, the serum IgG level is measured following administration of the FcRn antagonist weekly for 4 weeks. In some embodiments, the serum IgG level is measured following administration of the FcRn antagonist weekly for 16 weeks. In some embodiments, the serum IgG level is measured following administration of the FcRn antagonist weekly for 24 weeks.

**[00266]** In an embodiment, the subject is any human or non-human animal. In an embodiment, the subject is a human or non-human mammal. In an embodiment, the subject is a human.

## EXAMPLES

**[00267]** The following examples are offered by way of illustration, and not by way of limitation.

**Example 1: Investigation of efficacy and safety of efgartigimod in adult patients with primary Sjögren's syndrome (pSS)**

**[00268]** Primary Sjögren's syndrome (pSS) is a chronic, progressive autoimmune disease of unclear etiology, typically presented as an exocrinopathy. Along with symptoms of extensive dryness, manifestations include profound fatigue, chronic pain, extraglandular organ system involvement, and increased risk of lymphomas. pSS is characterized by mononuclear inflammatory infiltrates and IgG plasma cells in salivary and lacrimal glands that lead to irreversible destruction of the glandular tissue and is accompanied by sensation of dryness of mouth and eyes. B cells play a central role in the immunopathogenesis and exhibit signs of hyperactivity. In addition, autoantibodies can create immune complexes that maintain and amplify the production of IFN alpha. This combination results in a cycle of immune activation that leads to tissue damage. A hallmark of pSS is B cell hyperactivity, causing a vicious cycle of immune activation through cytokine production, antigen presentation, and autoantibody secretion, potentially causing tissue damage. Currently, no immunomodulatory treatment is available for pSS.

**[00269]** For many decades, the clinical needs for pSS have been left unresolved because of the rareness of the disease and the complexity of the underlying pathogenic mechanisms. It has become clear that B cell activation and development of autoantibodies play an important role in pSS.

**[00270]** This study aims to evaluate the effect of efgartigimod, an FcRn antagonist that can rapidly reduce IgG, including pathogenic antibodies. Efgartigimod has the potential to successfully treat pSS and improve disease manifestations by the reduction of IgG autoantibodies in pSS.

*A. Study design*

*Overall design*

**[00271]** This is a randomized, double-blinded, placebo-controlled, phase 2 study.

**[00272]** For participants not enrolling in the open-label extension (OLE) study, the total study duration is approximately 36 weeks comprising:

- Screening period of ≤ 4 weeks
- Treatment period of 24 weeks
- Follow-up period of 56 days.

**[00273]** For participants enrolling in the open-label extension (OLE) study, the total study duration is approximately 28 weeks comprising:

- Screening period of ≤ 4 weeks
- Treatment period of 24 weeks.

**[00274]** The study population is adult patients with pSS, per American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) 2016 classification criteria, with at least a moderate level of systemic disease activity (EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥ 5). Participants are randomized to receive efgartigimod 10 mg/kg or placebo in a 2:1 ratio, respectively. All participants receive efgartigimod IV 10 mg/kg or placebo once weekly for 24 weeks during the treatment period. IMP (efgartigimod or placebo) is administered in an approximately 1-hour IV infusion by site staff or a home nurse. The final dose is administered at week 23. At week 24, eligible participants may roll over into a single-arm OLE.

*Selection of primary and secondary endpoints*

**[00275]** This study aims to evaluate the efficacy and safety of efgartigimod compared to placebo in participants with pSS. The study design is randomized, double-blinded, and placebo-controlled to evaluate the effect of efgartigimod administered as an IV infusion compared to placebo. The study consists of a treatment period where all participants receive weekly IV infusions for 24 weeks. As there are no standardized approved therapies for pSS, the comparison to placebo is justified.

**[00276]** The primary endpoint is the effect of efgartigimod IV compared to placebo on CRESS (Composite of Relevant Endpoints for Sjögren's Syndrome; described further below). The CRESS composite measures systemic disease activity, patient-reported symptoms, tear gland function, salivary gland function, and serology, developed to assess treatment efficacy in participants with pSS. CRESS was selected as the primary efficacy endpoint because a composite is presumed to be more appropriate in demonstrating drug efficacy compared to an endpoint that reports on a single aspect of this heterogeneous disease. In randomized controlled studies that

previously showed negative primary endpoint results using ESSDAI, post hoc analysis of the study data using CRESS resulted in higher response rates in participants. Use of CRESS also resulted in decreased placebo response rates compared with the use of the ESSDAI minimal clinically important improvement, which is essential to demonstrating treatment efficacy.

**[00277]** The secondary endpoints complement the primary endpoint and provide additional information on efficacy (ESSDAI, clinical ESSDAI [clinESSDAI], EULAR Sjögren's syndrome Patient Reported Index [ESSPRI], Sjögren's Tool for Assessing Response [STAR] [all described further below]), histology, safety, PK, PD, and immunogenicity.

*End of study*

**[00278]** The end of study is defined as the date of the last participant's last visit. A participant has completed the study if the treatment period (or follow-up period, if applicable) has been completed.

- Participants rolling over to the OLE study complete this study at week 24.
- Participants not rolling over to the OLE study complete this study after the safety follow-up visit (SFV) or early discontinuation visit (EDV), as applicable. If a participant continued in the study after discontinuing IMP, this is week 24 or at the SFV (if permanent IMP discontinuation is <56 days from week 24).

*B. Study population*

**[00279]** Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

*Inclusion criteria*

**[00280]** Participants are eligible for study inclusion only if all of the following criteria apply:

- Reached age of consent when signing the informed consent form;
- Capable of providing signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and this protocol;
- Meets the following criteria:
    - ACR/EULAR 2016 pSS who met criteria ≤7 years before screening (see below);
    - ESSDAI ≥5;
    - Ro/SS-A positive;

- Residual salivary flow (unstimulated whole salivary flow (UWSF) rate >0 and/or stimulated whole salivary flow (SWSF) rate >0.10);

- Agree to use contraceptives consistent with local regulations regarding the methods of contraception for those participating in clinical studies and the following:
  - Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before receiving IMP.

**[00281]** The ACR/EULAR classification of pSS applies to any individual who meets the following inclusion and exclusion criteria and has a score of ≥4 when summing the weights from the items presented in **Table S1**.

**[00282]** ACR/EULAR pSS classification inclusion criteria apply to any patient with ≥1 symptom of ocular or oral dryness, defined as a positive response to ≥1 of the following questions:

- Have you had daily, persistent, troublesome dry eyes for more than 3 months?
- Do you have a recurrent sensation of sand or gravel in the eyes?
- Do you use tear substitutes more than 3 times a day?
- Have you had a daily feeling of dry mouth for more than 3 months?
- Do you frequently drink liquids to aid in swallowing dry food?

OR suspicion of pSS from the ESSDAI questionnaire (with ≥1 positive domain item).

**[00283]** Prior diagnosis of any of the following conditions would exclude diagnosis of pSS according to ACR/EULAR criteria and participation in pSS studies or therapeutic studies because of overlapping clinical features or interference with criteria tests:

- AIDS;
- Active hepatitis C infection (with positive PCR);
- Sarcoidosis;
- Amyloidosis;
- Graft-versus-host disease;
- History of head and neck radiation treatment;
- IgG4-related disease.

**Table S1. ACR/EULAR Classification Criteria for Primary Sjögren's Syndrome**

| Item | Weight/Score |
|---|---|
| Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1[a] | 3 |
| Anti-Ro/SS-A positive | 3 |
| OSS of ≥5 (or van Bijsterfeld score of ≥4) on at least 1 eye | 1 |
| Schirmer's test of ≤5 mm/5 minutes on at least 1 eye[b] | 1 |
| UWSF rate of ≤0.1 mL/min[b] | 1 |

ACR=American College of Rheumatology; EULAR=European Alliance of Associations for Rheumatology; OSS=ocular staining score; SS-A=Sjögren's syndrome–related antigen A; UWSF= unstimulated whole salivary flow

[a] A pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count (based on number of foci per 4 $mm^2$) should perform the histopathologic examination following a protocol by Daniels et al. Arthritis Rheumatol. 2011;63(7):2021-2030.

[b] Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications so that these components can be a valid measure of oral and ocular dryness.

*Exclusion criteria*

**[00284]** Participants are excluded from the study if any of the following criteria apply:

- Known autoimmune disease or any medical condition that, in the investigator's judgment, would interfere with an accurate assessment of clinical symptoms of pSS or puts the participant at undue risk;
- History of malignancy unless considered cured by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of IMP. Adequately treated participants with the following cancers may be included at any time:
    - Basal cell or squamous cell skin cancer;
    - Carcinoma in situ of the cervix;
    - Carcinoma in situ of the breast;
    - Incidental histological finding of prostate cancer (TNM stage T1a or T1b);
- Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection;
- Positive serum test at screening for an active infection with any of the following:
    - Hepatitis B virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HB surface antigen (HBsAg) or negative HBV DNA test;
    - Hepatitis C virus (HCV) based on HCV antibody assay unless a negative RNA test is available;

  - Human immunodeficiency virus (HIV) based on test results of a CD4 count of <200 cells/mm$^3$ that are associated with an AIDS-defining condition;
  - HIV based on test results of a CD4 count of ≥200 cells/mm$^3$ not adequately treated with antiviral therapy;
- Clinically significant disease, recent major surgery (within 3 months of screening), or intends to have surgery during the study; or any other condition that in the opinion of the investigator could confound the results of the study or put the participant at undue risk;
- Current participation in another interventional clinical study;
- Known hypersensitivity to IMP or 1 of its excipients;
- History (within 12 months of screening) of or current alcohol, drug, or medication abuse;
- Pregnant or lactating or intention to become pregnant during the study;
- Previous participation in an efgartigimod clinical study and treatment with ≥1 dose of IMP;
- Total IgG <4 g/L at screening;
- Secondary Sjögren's syndrome overlap syndromes where another confirmed autoimmune rheumatic or systemic inflammatory condition (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, inflammatory bowel disease) is the primary diagnosis;
- Positive SARS-CoV-2 PCR test at screening;
- Any severe systemic pSS manifestation that may put the participant at undue risk based on the investigator's opinion;
- Intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), or plasmapheresis/plasma exchange (PLEX) <12 weeks before screening or during screening;
- Live or live-attenuated vaccine <4 weeks before screening or during screening;
- Pilocarpine and/or any other pharmacological stimulant for salivary and lacrimal glands ≤4 weeks from screening or during screening;
- Systemic corticosteroids ≤4 weeks from screening or during screening;
- Antimalarials, conventional disease-modifying antirheumatic drugs (DMARDs), or Janus kinase (JAK) inhibitors ≤4 weeks from screening or during screening;
- Biologic DMARDs ≤24 weeks from screening or during screening;
- Nonbiologic IMP in another clinical study <12 weeks or 5 half-lives (whichever is longer) or a biologic IMP <24 weeks or 5 half-lives (whichever is longer) before screening or during screening;
- Chinese traditional medicine with known immunomodulatory action.

*C. IMP(s) and concomitant therapy*

**[00285]** Investigational medicinal product (IMP) is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

*IMP(s) administered*

**[00286]** The IMP in this study includes efgartigimod IV and matching placebo (with the same formulation but without the active ingredient of efgartigimod), as described in **Table S2**:

**Table S2. IMP(s) administered**

| **Intervention Label** | Efgartigimod IV | Placebo |
|---|---|---|
| **Intervention Name** | Efgartigimod IV | Placebo |
| **Intervention Description** | Sterile, colorless, clear concentrate solution for IV infusion efgartigimod 20 mg/mL, administered IV | Sterile, colorless, clear concentrate solution for infusion, with the same excipients as efgartigimod IV, but without the active ingredient (efgartigimod) |
| **Type** | Biologic | Placebo |
| **Dose Formulation** | Concentrate for solution for IV infusion | Concentrate for solution for IV infusion |
| **Unit Dose Strength(s)** | 20 mg/mL | Not applicable |
| **Dosage Level(s)** | 10 mg/kg weekly x24 weeks | Not applicable |
| **Route of Administration** | IV infusion | IV infusion |
| **Use** | Experimental | Placebo-comparator |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor |
| **Packaging and Labeling** | IMP provided in glass vials. Each vial labeled as required per country requirements | IMP provided in glass vials. Each vial labeled as required per country requirements |
| **Former Name** | ARGX-113 | Not applicable |

**[00287]** The 10 mg/kg efgartigimod dose is based on body weight, and the maximum total dose per efgartigimod infusion is 1200 mg for participants who weigh ≥120 kg. The dose level is recalculated for body weight changes of ±10%.

**[00288]** Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements [including Chinese traditional medicine]) or other specific categories of interest that the participant is receiving at the time of screening or receives during the study participation must be recorded and include the following information: reason for use, dates of administration (including start and end dates), and dosage information (*e.g.*, dose and frequency).

*Prohibited medications*

**[00289]** The following medications/treatments are prohibited while the participant receives IMP:

- SCIg or IVIg;
- PLEX;
- Live or live-attenuated vaccines;
- Pilocarpine and/or any other pharmacological stimulant for salivary and lacrimal glands;
- Systemic corticosteroids;
- Antimalarials, conventional DMARDs, JAK inhibitors;
- Biologic DMARDs (*e.g.*, rituximab, other monoclonal antibodies);
- Pharmacological topical ophthalmic agents (*e.g.*, NSAIDs, corticosteroids, cyclosporine);
- IMP in another clinical study;
- Chinese traditional medicine with known immunomodulatory action.

**[00290]** Anticholinergic agents are permitted if the dose is stable during the screening and treatment periods.

**[00291]** Topical symptomatic medications for pSS are permitted but restrictions apply:

- At the baseline, week 16, week 24, and EDV/IMP discontinuation visits, participants are required to withhold ophthalmic lubricants, ophthalmic lubricating ointments, hydroxyl cellulose ophthalmic inserts, and saliva substitutes before efficacy assessments are completed.

*D. Study assessments and procedures*

**Table S3. Schedule of activities**

| | SCR | Study week | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study day** | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | IMP d/c visit[b] | EDV[c] (≤7 d after final dose) | SFV[a] (56 d after final dose) |
| **±Days** | −28 to −2 | BL | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | ±1 | | +2 | ±3 |
| **Visits[d,e]** | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | NA | NA | NA |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical/ surgical history[f] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demography[g] | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination[h] | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Brief physical examination (symptom driven)[i] | | | X | X | | X | | | | X | | | | X | | | | X | | | | X | | | | X | X | X | X |
| Vital signs[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG | X | X | | | | | | | | | | | | | | | | X | | | | | | | | X | X | X | X |
| Randomization | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Glandular function** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| Study day | SCR | Study week | | |

| | SCR | Study week | | |

| | SCR | Study week | | |

[d] Visits 4, 6-8, 10-12, 14-16, 18-20, and 22-24 may be performed in the participant's home by a home nurse.
[e] Safety, efficacy, and predose sampling activities are performed before administering IMP.
[f] Medical/surgical history includes all significant findings, surgeries, and preexisting conditions (including allergies, if any) present at screening including start and end date, if known.
[g] Demographic characteristics comprise age, birth year, sex, race, and ethnicity (per local regulations). Race and ethnicity data are source verified only if permitted by local laws.
[h] Physical examination includes height and weight. Height is measured at the baseline visit only.
[i] The brief physical examination is symptom driven and is performed as necessary to assess the ESSDAI. It also includes weight.
[j] Vital signs are all measured before collecting any blood sample or administering IMP infusions.
[k] Parotid biopsy is collected for immunophenotyping, assessment of germinal centers, lymphoepithelial lesions, and gene expression profiling. Refer to additional information about gene expression profiling below.
[l] Screening laboratory tests is performed at a central laboratory.
[m] Pregnancy testing uses a highly sensitive serum test at screening, and a urine test at all subsequent visits before IMP administration. Local regulations are followed if more stringent or frequent testing is required.
[n] COVID-19 testing occurs within 72 hours of baseline. Participants are tested for SARS-CoV-2 if they are symptomatic or if applicable law requires testing. COVID-19 testing is performed at a central or local laboratory.
[o] Blood samples are taken predose preferably within 2 hours before administering IMP.
[p] Blood samples are collected for immunophenotyping, cytokine and chemokine profiles, C1q immune complexes, autoantibodies, complement activation, and gene expression profiling.
[q] Exploratory biomarkers that are measured by flow cytometry are not assessed at week 16.
[r] Blood for PK analyses is collected predose (preferably within 2 hours before the infusion) and postdose (within 30 minutes after the end of the infusion).
[s] Salivary samples are collected for evaluation of salivary proteins. Refer to additional information about autoantibody analysis below.
[t] The biological domain is blinded postbaseline and sites score only the clinical domains of the ESSDAI.
[u] Patient-reported outcome questionnaires are administered before any other study visit procedure where safe, and before discussions with staff about disease/treatment.
[v] The IMP is administered as an approximately 1-hour IV infusion. Participants are monitored for safety for ≥30 minutes after the end of IMP administration.
[w] AEs and use of concomitant therapies are continuously monitored from the time the ICF is signed until the last study-related activity.

*CRESS*

**[00292]** The primary efficacy endpoint is the proportion of responders on ≥3 of 5 items at week 24 using CRESS. CRESS was developed to assess treatment efficacy in participants with pSS. CRESS consists of the following items, with definitions of treatment response and lower disease activity:

- Systemic disease activity: as measured with clinESSDAI (see below)
  - Response is defined as a score of <5 points.
- Patient-reported symptoms: as measured with ESSPRI (see below)
  - Response is defined as a decrease of ≥1 point or ≥15% from baseline.
- Tear gland function: as measured with Schirmer's test (see below) and OSS (see below)
  - If Schirmer's test is ≤5 mm at baseline (abnormal), a response is defined as an increase of at least 5 mm from baseline. OR
  - If OSS is ≥3 points at baseline (abnormal), a response is defined as a decrease of at least 2 points from baseline. OR
  - If both OSS and Schirmer's scores are normal at baseline, a response is defined as no change that results in an abnormal OSS or Schirmer's score.
- Salivary gland function: as measured with UWSF (see below) and salivary gland ultrasonography (SGUS)
  - UWSF: at least 25% increase in score, or if score is 0 mL/min at baseline, any increase from baseline. OR
  - SGUS: at least 25% decrease in total Hocevar score from baseline.
- Serology: as measured with serum IgG and RF
  - Rheumatoid factor (RF): decrease of at least 25% from baseline. OR
  - IgG: reduction of at least 10% from baseline.

*Parotid Gland Histology*

**[00293]** A secondary efficacy measure is the relative amount of lymphocytic infiltrate that can be assessed with CD45 immunohistochemical staining of the parotid gland. Increased lymphocytic infiltrate positive for CD45 has been observed in parotid gland biopsies of participants with pSS. Additionally, the ratio of B/B+T cells are assessed as a secondary outcome measure.

**[00294]** Furthermore, the following are assessed in the parotid gland as exploratory measures:

- Changes in immunophenotype, including but not limited to plasma cells (IgA, IgG and IgM) per $mm^2$ parenchyma;
- Focus score;
- Number of germinal centers and lymphoepithelial lesions per $mm^2$ in parotid gland parenchyma;
- Gene expression:
    - Gene expression analysis may be conducted using RNA sequencing for genes relevant to the participant immune status and related pathways, including the IFN pathway, to understand the response to efgartigimod therapy. Testing is optional if it is categorized as genetic testing by local regulations.

*ESSDAI*

**[00295]** The ESSDAI was designed to measure disease activity in patients with pSS. The ESSDAI consists of 12 domains, 11 related to organ involvement (cutaneous, pulmonary, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, and lymphadenopathic) and 1 biological domain reflecting B-cell activity. The activity levels of each domain (range: 0-3 points) are multiplied by their respective weights (range: 1-6 points) to obtain the total score (**Table S4**).

**Table S4. ESSDAI: Domain and Item Definitions and Weights**

| Domain [Weight] | Activity level | Description |
|---|---|---|
| **Constitutional [3]** *Exclusion of fever of infectious origin and voluntary weight loss* | No=0 | Absence of the following symptoms |
| | Low=1 | Mild or intermittent fever (37.5-38.5 °C)/night sweats and/or involuntary weight loss of 5 to 10% of body weight |
| | Moderate=2 | Severe fever (>38.5 °C)/night sweats and/or involuntary weight loss of >10% of body weight |
| **Lymphadenopathy [4]** *Exclusion of infection* | No=0 | Absence of the following features |
| | Low=1 | Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region |
| | Moderate=2 | Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) |
| | High=3 | Current malignant B-cell proliferative disorder |

| Domain [Weight] | Activity level | Description |
|---|---|---|
| **Glandular [2]** *Exclusion of stone or infection* | No=0 | Absence of glandular swelling |
| | Low=1 | Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling |
| | Moderate=2 | Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling |
| **Articular [2]** *Exclusion of osteoarthritis* | No=0 | Absence of currently active articular involvement |
| | Low=1 | Arthralgias in hands, wrists, ankles, and feet, accompanied by morning stiffness (>30 minutes) |
| | Moderate=2 | 1 to 5 (of 28 total count) synovitis |
| | High=3 | ≥6 (of 28 total count) synovitis |
| **Cutaneous [3]** *Rate as "No activity" stable long-lasting features related to damage* | No=0 | Absence of currently active cutaneous involvement |
| | Low=1 | Erythema multiforme |
| | Moderate=2 | Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus |
| | High=3 | Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis |
| **Pulmonary [5]** *Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)* | No=0 | Absence of currently active pulmonary involvement |
| | Low=1 | Persistent cough or bronchial involvement with no radiographic abnormalities on radiography; or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test |
| | Moderate=2 | Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% > DLCO ≥ 40% or 80% > FVC ≥ 60% |
| | High=3 | Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: 70% > DLCO ≥ 40% or 80% > FVC ≥ 60% |
| **Renal [5]** *Rate as "No activity" stable long-lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate* | No=0 | Absence of currently active renal involvement with proteinuria <0.5 g/day, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage |
| | Low=1 | Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without hematuria or renal failure (GFR ≥60 mL/min) |

| Domain [Weight] | Activity level | Description |
|---|---|---|
| *activity based on histological features first* | Moderate=2 | Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without hematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate |
| | High=3 | Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or hematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement |
| **Muscular [6]** *Exclusion of weakness due to corticosteroids* | No=0 | Absence of currently active muscular involvement |
| | Low=1 | Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N < CK ≤ 2N) |
| | Moderate=2 | Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N) |
| | High=3 | Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N) |
| **PNS [5]** *Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease* | No=0 | Absence of currently active PNS involvement |
| | Low=1 | Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia |
| | Moderate=2 | Moderately active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, CIDP with mild functional impairment (maximal motor deficit of 4/5or mild ataxia), or cranial nerve involvement of peripheral origin (except trigeminal [V] neuralgia) |
| | High=3 | Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc.), severe ataxia due to ganglionopathy, CIDP with severe functional impairment: motor deficit ≤3/5 or severe ataxia |
| **CNS [5]** *Rate as "No activity" stable long-lasting features related to damage or CNS* | No=0 | Absence of currently active CNS involvement |
| | Low=1 | Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis, or multiple sclerosis–like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment |

| Domain [Weight] | Activity level | Description |
|---|---|---|
| *involvement not related to the disease* | High=3 | Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis–like syndrome with motor deficit |
| **Hematological [2]** *For anemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia* | No=0 | Absence of autoimmune cytopenia |
| | Low=1 | Cytopenia of autoimmune origin with neutropenia ($1000 < \text{neutrophils} < 1500/mm^3$), and/or anemia ($10 < \text{hemoglobin} < 12$ g/dl), and/or thrombocytopenia ($100\,000 < \text{platelets} < 150\,000/mm^3$); or lymphopenia ($500 < \text{lymphocytes} < 1000/mm^3$) |
| | Moderate=2 | Cytopenia of autoimmune origin with neutropenia ($500 \leq \text{neutrophils} \leq 1000/mm^3$), and/or anemia ($8 \leq \text{hemoglobin} \leq 10$ g/dl), and/or thrombocytopenia ($50\,000 \leq \text{platelets} \leq 100\,000/mm^3$); or lymphopenia ($\leq 500/mm^3$) |
| | High=3 | Cytopenia of autoimmune origin with neutropenia (neutrophils $<500/mm^3$) and/or anemia (hemoglobin <8 g/dl) and/or thrombocytopenia (platelets $<50\,000/mm^3$) |
| **Biological [1]** | No=0 | Absence of any of the following biological features |
| | Low=1 | Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L |
| | Moderate=2 | Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L) |

CIDP=chronic inflammatory demyelinating polyneuropathy; CK=creatine kinase; CNS=central nervous system; DLCO=diffusing capacity of the lungs for carbon monoxide; EMG=electromyogram; ESSDAI=EULAR Sjögren's syndrome disease activity index; FVC=forced vital capacity; GFR=glomerular filtration rate; HRCT=high-resolution computed tomography; IgG=immunoglobulin G; N=normal; NCS=nerve conduction studies; NHYA=New York Heart Association (classification); PNS=peripheral nervous system

*ClinESSDAI*

**[00296]** ClinESSDAI derives from the ESSDAI, and its score provides an accurate evaluation of disease activity independent of B-cell biomarkers. The clinical domains in clinESSDAI have different weights than in ESSDAI (**Table S5**).

**Table S5. Comparison of Domain Weights of Original ESSDAI and clinESSDAI**

| Domain (activity level) | ESSDAI | clinESSDAI |
|---|---|---|
| Constitutional (0-2) | 3 | 4 |
| Lymphadenopathy (0-3) | 4 | 4 |
| Glandular (0-2) | 2 | 2 |

| Domain (activity level) | ESSDAI | clinESSDAI |
|---|---|---|
| Articular (0-3) | 2 | 3 |
| Cutaneous (0-3) | 3 | 3 |
| Pulmonary (0-3) | 5 | 6 |
| Renal (0-3) | 5 | 6 |
| Muscular (0-3) | 6 | 7 |
| Peripheral nervous system (0-3) | 5 | 5 |
| Central nervous system (0-3) | 5 | 5 |
| Hematological (0-3) | 2 | 2 |
| Biological (0-2) | 1 | NA |
| Score total | 0-123 | 0-135 |

clinESSDAI=clinical EULAR Sjögren's syndrome disease activity index; ESSDAI=EULAR Sjögren's syndrome disease activity index; EULAR= European Alliance of Associations for Rheumatology; NA=not applicable

*STAR*

**[00297]** STAR was developed to assess the efficacy of treatments for pSS. A secondary efficacy endpoint for this study is the proportion of responders (STAR score of ≥5) at week 24.

**[00298]** This composite measure contains 5 domains:

- Systemic activity: 3 points
    - clinESSDAI decrease of ≥3 points;
- Patient-reported outcome: 3 points
    - ESSPRI decrease of at least 1 point or ≥15% (see below)
    - Symptoms of dryness, pain, and fatigue rated on 3 numeric rating scales;
- Lacrimal gland function (assessed by Schirmer's test or OSS): 1 point
    - Schirmer's test (see below)
        - If abnormal score at baseline: increase of ≥5 mm from baseline;
        - If normal score at baseline: no change to abnormal;
    - OSS (see below)
        - If abnormal score at baseline: decrease of ≥2 points from baseline;
        - If normal score at baseline: no change to abnormal;
- Salivary gland function: 1 point
    - UWSF:
        - If score >0 at baseline: increase of ≥25% from baseline;

- If score is 0 at baseline: any increase in UWSF from baseline;

OR

- SGUS:
  - ≥25% decrease in total Hocevar score from baseline;

- Biological (assessed by IgG or RF): 1 point
  - IgG: ≥10% reduction;
  - RF: ≥25% decrease.

*Patient-Reported Outcomes*

*ESSPRI*

**[00299]** ESSPRI is a questionnaire developed to measure self-reported symptoms in participants with pSS. The ESSPRI has 3 items that measure dryness, fatigue, and pain over a recall period of "the last 2 weeks." Each item includes a numeric rating scale ranging from 0 "No symptoms (dryness, fatigue or pain)" to 10 "Maximal imaginable (dryness, fatigue or pain)." The total global score ranges from 0 to 10 and the ESSPRI is calculated by averaging the numeric scores for pain, fatigue, and dryness, with higher scores indicating more symptoms. It has been shown to correlate well with PGA and has been validated in participants with pSS.

*MFI*

**[00300]** The MFI is a 20-item scale designed to evaluate 5 dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. Participants are asked to report their fatigue over a recall period of "lately" (past 7 days). Each item in the MFI includes 5 boxes ranging from "yes, that is true" to "no, that is not true," and participants are asked to indicate how true certain statements are in regard to their experience with fatigue. Scores in each domain range from 4 to 20, with lower scores corresponding to better health status.

*PGA*

**[00301]** PGA is a tool that measures a participant's global evaluation of their overall disease activity at the time of assessment.

**[00302]** The participant rates their overall disease activity by drawing a vertical mark on a 10-cm VAS from the left end of the line (no evidence of disease activity) to the right end of the line (extremely active or severe disease activity).

*SF-36*

**[00303]** The SF-36 is a 36-item scale constructed to survey health-related quality of life on 8 domains: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue); and general health perceptions. The SF-36 includes Yes/No questions in addition to 3 point, 5 point, or 6 point Likert response scales. Participants are required to complete the SF-36 using the recall period of "the last 4 weeks." SF-36 scores are calculated by domain, and total calculated scores for each domain can range from 0 to 100, with higher scores being equated to better health status. The SF-36 is scored into 2 summary scores: physical component summary (consisting of physical function, physical role, bodily pain, and general health domain total scores) and mental component summary (consisting of vitality, mental health, role emotional, and social function domain total scores).

*PASS*

**[00304]** PASS is a patient-reported outcome measure that assesses the "value beyond which patients consider themselves well." PASS measures participant well-being and overall feeling that symptoms are in remission, through a single question that is dependent on the indication.

**[00305]** PASS assesses the level of symptoms at which participants with rheumatic diseases consider themselves well. To record the PASS, the rheumatologist asks the participant whether they consider their current state to be satisfactory, considering all of the consequences of their disease.

*EQ-5D-5L*

**[00306]** EQ-5D-5L is a standardized measure of health status. It was developed by the EuroQol Group to provide a simple, generic measure of health status for clinical and economic appraisal. The descriptive system comprises 5 dimensions:

- Mobility;
- Self-care;
- Usual activities;

- Pain/discomfort;
- Anxiety/depression.

**[00307]** Each dimension has 5 levels:

- No problem;
- Slight problem;
- Moderate problem;
- Severe problem;
- Extreme problem.

**[00308]** The participant is asked to indicate their health state by selecting the box next to the most appropriate statement in each of the 5 dimensions using the recall period "today." This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions were combined in a 5-digit number describing the respondent's health state. A unique health state is defined by combining 1 level from each of the 5 dimensions. A total of 3125 possible health states could be defined in this way. Each state is referred to in terms of a 5-digit code. For example, state 11111 would indicate no problems in any of the 5 dimensions, and 12345 would indicate no problem with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression.

**[00309]** A VAS is included in the questionnaire. Respondents are asked to mark the health status from 0 to 100 on the day the interview is conducted, with a score of 0 corresponding to "the worst health you can imagine" and 100 corresponding to "the best health you can imagine."

*Additional Efficacy Measures*

*SGUS*

**[00310]** The SGUS grading system of Hocevar et al. rates 5 parameters: parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hypoechogenic reflections, and the clearness of salivary gland borders. The overall ultrasound score is calculated by summation of the grades for the 5 subscores for all 4 major salivary glands. The overall ultrasound score can range from 0 to 48.

*Salivary Flow Rate*

**[00311]** SWSF and UWSF rates are assessed in this study.

*Schirmer's Test*

**[00312]** Schirmer's test is an assessment of tear gland function in which a strip of filter paper is applied under the eyelid to measure the quantity of tear production. A result of ≤5 mm indicates abnormal tear gland function.

*OSS*

**[00313]** OSS is used in this study to assess tear gland function in participants with pSS. OSS uses lissamine green dye to grade the conjunctiva, and fluorescent dye to grade the cornea. A score of ≥3 points indicates abnormal tear gland function.

*E. Pharmacokinetics*

**[00314]** Blood samples for PK analysis are collected predose on IMP administration visits (preferably within the 2 hours before IMP infusion) and within the 30 minutes after the end of the infusion as described in **Table S3**. Efgartigimod serum concentrations are determined using a validated method.

*F. Pharmacodynamics*

**[00315]** Baseline and postbaseline PD blood samples are collected predose, preferably within 2 hours before IMP administration at the time points described in **Table S3**.

**[00316]** Total IgG levels are determined using validated methods at a central laboratory. IgG is assessed at screening as part of the eligibility criteria and secondary efficacy measures.

**[00317]** Participants are also tested for anti-Ro/SS-A and anti-La/SS-B autoantibodies at the time points described in **Table S3**, as a part of inclusion criteria requirements and secondary efficacy measures.

*G. Biomarkers*

**[00318]** Blood is collected, whereas serum and PBMCs are aliquoted at the time points described in **Table S3** to explore the relation between relevant biomarkers and clinical effects.

**[00319]** PBMCs are used for immunophenotyping using flow cytometry, including but not limited to the assessment of the proportion of B cells within the CD45+ population. In addition, these samples may be analyzed for changes in gene expression. Gene expression analysis is conducted using RNA sequencing for genes relevant to participant immune status and related

pathways, including the IFN pathway, to understand participant response to efgartigimod therapy. This is performed only if both efficacy and biomarker data support the hypothesis. Testing is optional if it is categorized as genetic testing by local regulations.

**[00320]** Serum is used for the analysis of autoantibodies, immune complexes, quantification of chemokines/cytokines, and markers of complement activation (including but not limited to C3, C4, and/or split products thereof).

**[00321]** Saliva is collected at the time points described in **Table S3** to explore the relation between salivary proteins and clinical effects.

*H. Immunogenicity assessments*

**[00322]** Blood samples are collected predose (within the 2 hours before IMP infusion) at the time points described in **Table S3** to evaluate the serum levels of ADAs against efgartigimod.

**[00323]** Samples are analyzed by the designated laboratory in a tiered approach using validated immunogenicity assays.

*I. Objectives and endpoints*

**Table S6. Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the effect of efgartigimod IV compared to placebo on CRESS | • Proportion of CRESS responders on ≥3 of 5 items at week 24. The 5 items are:<br>– Systemic disease activity: clinESSDAI<br>– Patient-reported symptoms: ESSPRI<br>– Tear gland function: Schirmer's test and OSS<br>– Salivary gland function: UWSF rate and SGUS<br>– Serology (serum IgG and/or RF) |
| **Secondary** | |
| • To evaluate the effect of efgartigimod IV compared to placebo on the histology of the parotid gland | • Change in the relative counts of lymphocytic infiltrate (stained for CD45) at week 24<br>• Change in B/B+T cell ratio at week 24 |
| • To evaluate the safety of efgartigimod IV compared to placebo in participants with pSS | • Incidence and severity of TEAEs, AESIs, and SAEs by SOC and PT<br>• Changes in vital sign measurements, ECG results, and clinical laboratory safety evaluations |

| Objectives | Endpoints |
|---|---|
| • To evaluate the effect of efgartigimod IV compared to placebo on clinical efficacy parameters | • Proportion of participants with minimal clinically important improvement in ESSDAI: improvement of ≥3 points in ESSDAI score at week 24<br>• Proportion of participants with low disease activity: ESSDAI score of <5 at week 24<br>• Proportion of participants with minimal clinically important improvement in clinESSDAI: improvement of ≥3 points in clinESSDAI score at week 24<br>• Proportion of participants with low disease activity: clinESSDAI score of <5 at week 24<br>• Proportion of participants with minimal clinically important improvement in ESSPRI: decrease of 1 point or ≥15% at week 24<br>• Change in ESSDAI score at week 24<br>• Change in clinESSDAI score at week 24<br>• Change in ESSPRI score at week 24 |
| • To evaluate the effect of efgartigimod IV compared to placebo on STAR | • Proportion of participants with STAR score of ≥5 at week 24 |
| • To evaluate the PK of efgartigimod IV | • Efgartigimod serum concentration-time profile |
| • To evaluate the PD of efgartigimod IV | • Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum<br>• Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum:<br>– Anti-Ro/ SS-A<br>– Anti-La/ SS-B |
| • To evaluate the immunogenicity of efgartigimod IV | • Incidence and prevalence of ADA against efgartigimod in serum |
| **Exploratory** | |
| • To explore the effect of efgartigimod IV compared to placebo on additional clinical pSS measures | • Proportion of responders on 2 of 4 items of the adjusted CRESS (without serology item) at week 24<br>• Change in activity of individual ESSDAI domains at week 24 |
| • To explore the effect of efgartigimod IV compared to placebo on glandular measures | • Change in SWSF rate at week 24<br>• Change in UWSF rate at week 24<br>• Change in Hocevar score at week 24<br>• Change in Schirmer's test at week 24<br>• Change in OSS at week 24<br>• Response in salivary gland as defined in CRESS at week 24 |

| Objectives | Endpoints |
|---|---|
| | • Response in tear gland as defined in CRESS at week 24 |
| • To explore the effect of efgartigimod IV compared to placebo on patient-reported outcomes | • Change in total MFI score at week 24<br>• Change in physical component and mental component scores of SF-36 at week 24<br>• Change in PGA at week 24<br>• Change in individual ESSPRI scores at week 24<br>• Change in EQ-5D-5L utilities score at week 24<br>• Change in VAS score at week 24<br>• PASS at week 24 |
| • To explore the effect of efgartigimod IV compared to placebo on additional histological measures on parotid gland biopsy | • Changes in immunophenotype, focus score, number of germinal centers, lymphoepithelial lesions, and gene expression per $mm^2$ in parotid gland parenchyma at week 24 |
| • To explore the effect of efgartigimod IV compared to placebo on serum biomarkers | • Change in cytokine/chemokine profiles (including but not limited to BAFF, type 1 interferon [IFN]) at weeks 4, 16, and 24<br>• Reduction in C1q immune complexes at weeks 4, 16, and 24<br>• Reduction in IgA, IgM, and IgG-related autoantibodies at weeks 4, 16, and 24<br>• Values, changes from baseline, and percent reduction from baseline in RF in serum<br>• Reduction in serum markers of complement activation (including but not limited to C3, C4, and/or split products thereof) at weeks 4, 16, and 24 |
| • To explore the effect of efgartigimod IV compared to placebo on blood biomarkers | • Change in immunophenotyping in peripheral blood using flow cytometry at weeks 4 and 24<br>• Change in gene expression profile (RNA sequencing) at weeks 4, 16, and 24 |
| • To explore the effect of efgartigimod IV compared to placebo on saliva biomarkers | • Change in salivary proteins at weeks 4, 16, and 24 |

**Example 2: Results from Phase 2 proof-of-concept study to evaluate efficacy and safety of efgartigimod in adult patients with pSS (rho)**

**[00324]** For the rho phase 2 study described in Example 1, 51 patients were assessed for eligibility. Of these, 34 participants were randomized into the study and 17 were considered screening failures (anti-Ro negative: 3; withdrew consent/lost FU: 4; > 7 years since diagnosis: 1; background treatment: 2; low systemic disease: 2; concurrent disease: 3; not specified: 2). Of the

34 participants randomized, 16 participants had a baseline serum IgG <16 g/L and 18 participants had a baseline serum IgG ≥16 g/L. 11 participants were randomized to receive placebo and 23 participants were randomized to receive efgartigimod. In the placebo group, 2 participants were excluded from the efficacy analysis set (EAS) due to prohibited medications at baseline. In the efgartigimod group, 1 participant was excluded from the EAS due to prohibited medications at baseline. Ultimately, 7 participants in the placebo group completed both the trial and treatment; 20 participants in the efgartigimod group completed the trial and 18 participants completed treatment.

**[00325]** Demographic characteristics were generally comparable between the efgartigimod and placebo groups (Table S7). Most participants were white, female, and between 18-65 years of age.

**[00326]** There were slight differences in some baseline characteristics between the efgartigimod and placebo groups (Table S8). Slightly higher ESSDAI, higher OSS, lower Schirmer, lower salivary flow, and longer disease duration values were seen at baseline in the placebo group vs. the efgartigimod group. These baseline characteristics were more balanced in the EAS.

**[00327]** Concomitant treatment was stable per protocol (Table S9). Use of DMARDs and corticosteroids 12 weeks before screening, during screening, and during the IMP period was controlled with extensive prohibited medications list. 3 participants were discontinued because of prohibited medication at screening and excluded from EAS; 1 participant was discontinued during the trial because of prohibited medication (MMF week 21) after baseline; and 1 patient discontinued treatment due to additional steroid use but completed study (potential impact of steroids on ESSDAI).

**Table S7. Participant Demographics**

| | | Efgartigimod (N=23) | Placebo (N=11) | All Participants (N=34) |
|---|---|---|---|---|
| **Age (years)** | Mean (SD) | *50.1 (12.57)* | *54.7 (12.42)* | *51.6 (12.52)* |
| | Median (min, max) | *49.0 (29.0, 69.0)* | *58.0 (37.0, 70.0)* | *49.0 (43.0, 64.0)* |
| **Age Category (years)** | 18 -<65 years | 18 (78.3) | 8 (72.7) | 26 (76.5) |
| | 65- <75 years | 5 (21.7) | 3 (27.3) | 8 (23.5) |
| | ≥75 years | 0 | 0 | 0 |
| **Sex at birth, n (%)** | Female | *22 (95.7)* | 11 (100) | *33 (97.1)* |
| | Male | *1 (4.3)* | *0* | *1 (2.9)* |
| **Weight, kg** | Mean (SD) | *64.57 (12.778)* | *64.32 (13.255)* | *64.49 (12.732)* |
| | Median (min, max) | *66.40 (45.0, 104.5)* | *66.00 (48.6, 94.5)* | *66.20 (45.0, 104.5)* |
| **BMI, kg/m²** | Mean (SD) | *23.90 (4.346)* | *24.15 (4.814)* | 23.98 (4.431) |
| | Median (min, max) | *23.30 (18.2, 38.4)* | *23.10 (18.6, 34.1)* | *23.20 (18.2, 38.4)* |
| **Race, n (%)** | White | *22 (95.7)* | *11 (100)* | 33 (97.1) |
| | Other | *1 (4.3)* | 0 | 1 (2.9) |
| **Ethnicity, n (%)** | Hispanic or Latino | 0 | 0 | 0 |
| | Not Hispanic or Latino | 22 (95.7) | 11 (100) | 33 (97.1) |
| | Unknown | 1 (4.3) | 0 | 1 (2.9) |

**Table S8. Baseline Disease Characteristics**

| | | Efgartigimod (N=23) | Placebo (N=11) | All Participants (N=34) |
|---|---|---|---|---|
| **Time since pSS diagnosis (years)** | Mean (SD) | *4.0 (3.71)* | *7.3 (6.18)* | *5.0 (4.82)* |
| | Median (min, max) | *3.0 (1, 18)* | *6.0 (2, 24)* | *4.0 (1, 24)* |
| **Time since ACR-EULAR Classification time (years)** | Mean (SD) | 3.0 (2.16) | 5.5 (3.11) | 3.8 (2.71) |
| | Median (min, max) | 2.0 (1, 7) | 6.0 (1, 12) | 3.5 (1, 12) |
| **UWSF (g/min)** | N | 23 | 11 | 34 |
| | Mean (SD) | 0.1566 (0.23037) | 0.09999 (0.04403) | 0.1383 (0.19155) |
| | Median (min, max) | 0.1160 (0.016, 1.172) | 0.0980 (0.024, 0.172) | 0.1030 (0.016, 1.172) |
| **SWSF (g/min)** | N | 23 | 11 | 34 |
| | Mean (SD) | 0.3987 (0.44932) | 0.2022 (0.16823) | 0.3351 (0.38972) |
| | Median (min, max) | 0.2300 (0.046, 1.873) | 0.1540 (0.010, 0.610) | 0.2145 (0.010, 1.873) |
| **OSS – Whitcher Right Eye** | N | 21 | 9 | 30 |
| | Mean (SD) | 4.5 (3.31) | 5.3 (3.00) | 4.7 (3.19) |
| | Median (min, max) | 4.0 (0, 11) | 5.0 (0, 9) | 4.5 (0, 11) |
| **OSS – Whitcher Left Eye** | N | 21 | 9 | 30 |
| | Mean (SD) | 4.2 (3.60) | 5.8 (3.70) | 4.7 (3.64) |
| | Median (min, max) | 3.0 (0, 11) | 6.0 (0, 12) | 5.5 (0, 12) |
| **Schirmer – right eye (mm/5min)** | N | 23 | 11 | 34 |
| | Mean (SD) | 4.4 (4.43) | 3.5 (3.11) | 4.1 (4.03) |
| | Median (min, max) | 3.0 (1, 20) | 3.0 (0, 11) | 3.0 (0, 20) |
| **Schirmer – left eye (mm/5min)** | N | 23 | 11 | 34 |
| | Mean (SD) | 4.0 (3.20) | 4.1 (3.14) | 4.0 (3.13) |
| | Median (min, max) | 4.0 (0, 15) | 3.0 (0, 10) | 3.0 (0, 15) |
| **Schirmer <5mm/5min in at least 1 eye** | N | 23 | 11 | 34 |
| | Yes | 18 ( 78.3) | 9 ( 81.8) | 27 ( 79.4) |
| | No | 5 (21.7) | 2 (18.2) | 7 (20.6) |

| | | Efgartigimod (N=23) | Placebo (N=11) | All Participants (N=34) |
|---|---|---|---|---|
| **Rheumatoid Factor** | N | 18 | 9 | 27 |
| | Mean (SD) | 71.6 (85.64) | 111.8 (116.18) | 85.0 (96.55) |
| | Median (min, max) | 51.0 (10, 385) | 59.0 (12, 360) | 59.0 (10, 385) |
| **ESSDAI Total score** | N | 23 | 11 | 34 |
| | Mean (SD) | 13.1 (5.77) | 16.5 (8.54) | 14.2 (6.85) |
| | Median (min, max) | 12.0 (6, 28) | 17.0 (8, 33) | 12.5 (6, 33) |
| **ESSDAI ≥10** | N | 23 | 11 | 34 |
| | Yes | 16 (69.6) | 7 (63.6) | 23 (67.6) |
| | No | 7 (30.4) | 4 (36.4) | 11 (32.4) |
| **ClinESSDAI Total Score** | N | 23 | 11 | 34 |
| | Mean (SD) | 14.3 (6.60) | 17.6 (8.99) | 15.4 (7.48) |
| | Median (min, max) | 13.0 (5, 30) | 18.0 (7, 36) | 14.0 (5, 36) |
| **ESSPRI Score** | N | 20 | 8 | 28 |
| | Mean (SD) | 6.484 (1.2222) | 5.416 (0.9869) | 6.179 (1.2430) |
| | Median (min, max) | 6.670 (3.00, 8.00) | 5.000 (4.33, 7.00) | 6.330 (3.00, 8.00) |

| | | Efgartigimod (N=23) | Placebo (N=11) | All Participants (N=34) |
|---|---|---|---|---|
| **MFI score** | N | 20 | 8 | 28 |
| | Mean (SD) | 64.7 (11.58) | 56.1 (11.61) | 62.2 (12.03) |
| | Median (min, max) | 65.5 (39, 85) | 54.0 (39, 80) | 63.0 (39, 85) |
| **Baseline IgG** | N | 23 | 11 | 34 |
| | Mean (SD) | 18.131 (8.0973) | 16.087 (5.3647) | 17.470 (7.3057) |
| | Median (min, max) | 17.320 (8.21, 42.33) | 17.750 (8.89, 26.72) | 17.340 (8.21, 42.33) |
| **Baseline IgA** | N | 23 | 11 | 34 |
| | Mean (SD) | 2.510 (1.0511) | 2.471 (0.6314) | 2.497 (0.9261) |
| | Median (min, max) | 2.280 (1.28, 5.27) | 2.370 (1.75, 3.41) | 2.290 (1.28, 5.27) |
| **Baseline IgM** | N | 23 | 11 | 34 |
| | Mean (SD) | 1.109 (0.7828) | 1.662 (1.7936) | 1.288 (1.2051) |
| | Median (min, max) | 0.910 (0.28, 3.63) | 0.910 (0.33, 5.88) | 0.910 (0.28, 5.88) |
| **Anti-Ro/SS-A Positive** | N | 23 | 11 | 34 |
| | Mean (SD) | 216.732 (60.4181) | 207.106 (73.3625) | 213.618 (63.9170) |
| | Median (min, max) | 240.000 (32.72, 240.00) | 240.000 (47.64, 340.00) | 240.000 (32.72, 240.00) |
| **Anti-La/SS-B positive** | N | 23 | 11 | 34 |
| | Mean (SD) | 107.407 (145.9732) | 182.394 (159.8528) | 131.668 (152.3702) |
| | Median (min, max) | 7.180 (0.4, 320.00) | 320.000 (0.40, 320.00) | 19.120 (0.40, 320.00) |

**Table S9. Concomitant Therapy**

| | Efgartigimod (N=23) n (%) | Placebo (N=11) n (%) | All Participants (N=34) n (%) |
|---|---|---|---|
| **Any therapies taken** | 23 (100.0) | 11 (100.0) | 34 (100.0) |
| **Sjogren's treatments (DMARDs and systemic corticosteroids** | | | |
| **DMARDs** | 15 (65.2) | 9 (81.8) | 24 (70.6) |
| Hydroxychloroquine | 12 (52.2) | 5(45.5) | 17 (50.0) |
| Chloroquine Phosphate | 0 | 3 ( 27.3) | 3 (8.8) |
| Methotrexate | 2 (8.6) | 1 (9.1) | 2 (5.9) |
| Azathioprine | 0 | 1 (9.1) | 1 (2.9) |
| Mycophenolate Mofetil | 1 (4.3) | 0 | 1 (2.9) |
| **Corticosteroids For Systemic Use, Plain** Methylprednisolone | 7 (30.4) | 2 (18.2) | 9 (26.5) |
| **Symptomatic treaments** | | | |
| **Dermatologicals, Topical Corticosteroids** | 7 (30.4) | 0 | 7 (20.6) |
| **Antiinflammatory and Antirheumatic Products, Non-Steroids** | 7 (30.4) | 5 (45.5) | 12 (35.3) |

**[00328]** *Primary Endpoint*

**[00329]** As discussed in Example 1, CRESS was chosen as the primary endpoint for the rho study. A clear effect of efgartigimod was seen on CRESS response, with 45% (10/22) of participants in the efgartigimod group achieving CRESS response vs. 11% (1/9) of participants in the placebo group achieving CRESS response at week 24.

**[00330]** An effect of efgartigimod could be seen in 4 of the 5 components that make up the CRESS composite, as shown in Table S10.

**Table S10. Individual CRESS Component Responses**

| CRESS Component | Efgartigimod (% responders) | Placebo (% responders) |
|---|---|---|
| ClinESSDAI | 59% (13/22) | 33% (3/9) |
| ESSPRI | 32% (7/22) | 33% (3/9) |
| Tear Gland | 27% (6/22) | 11% (1/9) |
| Salivary Gland | 36% (8/22) | 22% (2/9) |
| Serology | 86% (19/22) | 11% (1/9) |

ClinESSDAI response = score of < 5 points; ESSPRI response = decrease of ≥ 1 point or ≥ 15%; Tear Gland response = increase of ≥5 mm in Schirmer's test if abnormal (≤ 5 mm) at baseline; OR decrease of ≥ 2 points in OSS if abnormal (≥ 3 points) at baseline; OR if both scores are normal at baseline, no change to abnormal; Salivary Gland response = UWSF: at least 25% increase in score, or if score is 0 mL/min, any increase OR SGUS: at least 25% decrease in total Hocevar score; Serology response = serum RF: Decrease of at least 25% from baseline OR serum IgG: Decrease of at least 10% from baseline

**[00331]** Of the 6 participants in the efgartigimod group that achieved tear gland response, 1 participant had an increase ≥5 mm in Schirmer's test if abnormal (≤ 5 mm) at baseline; 4 participants had a decrease of ≥ 2 points in OSS if abnormal (≥ 3 points) at baseline; and 1 participant was normal for Schirmer's and OSS at baseline and remained normal. The 1 participant in the placebo group that achieved tear gland response had a decrease of ≥ 2 points in OSS if abnormal (≥ 3 points) at baseline.

**[00332]** Of the 8 participants in the efgartigimod group that achieved salivary gland response, 7 participants had at least 25% increase in UWSF from baseline and 4 participants had at least 25% in Hocevar score from baseline. The 2 participants in the placebo group that achieved salivary gland response had at least 25% increase in UWSF from baseline.

**[00333]** All of the ESSPRI responders in both groups had a decrease of ≥ 1 point and a decrease of ≥ 15% from baseline.

**[00334]** *STAR*

**[00335]** The STAR composite is similar to the CRESS composite in that both globally assess the disease by evaluating the same 5 components but weigh them differently (see Table S11).

**Table S11. CRESS vs. STAR**

| Items | CRESS | STAR* |
|---|---|---|
| Systemic disease activity (clinESSDAI) | 1 (score of < 5 points) | 3 (decrease of ≥ 3 points) |
| Patient-reported symptoms (ESSPRI) | 1 | 3 |
| Tear gland function (Shirmer's or OSS) | 1 | 1 |
| Salivary gland function (UWSF or SGUS) | 1 | 1 |
| Serology (RF or IgG) | 1 | 1 |
| Total response defined as | Responder per ≥ 3 of 5 items | Score of ≥ 5 |

* STAR requires response in ESSPRI or ClinESSDAI to be a responder

**[00336]** In the efgartigimod group, 55% (12/22) were STAR responders at 24 weeks, whereas in the placebo group, only 33% (3/9) were STAR responders.

**[00337]** *ClinESSDAI*

**[00338]** ClinESSDAI results at week 24 are shown in Table S12. Within the efgartigimod group, 6 participants with high disease activity at baseline (>13) gradually improved to moderate (5-13) or low (<5) disease activity; 2 participants with high disease activity at baseline showed no response; 9 participants with moderate disease activity at baseline improved to low disease and 2 participants with moderate disease activity at baseline remained moderate. In the placebo group, 2 participants with high disease activity at baseline improved to low disease activity; 2 participants with high disease activity at baseline fluctuated between low and moderate; 1 participant with moderate activity at baseline improved to low disease activity; and 2 participants with moderate disease activity remained moderate. A higher % of responders was seen in the efgartigimod group based on a decrease in ClinESSDAI of ≥5 points.

**Table S12. ClinESSDAI Results**

| | Actual Values | | Change from Baseline | |
|---|---|---|---|---|
| **Domain / Visit** | **Efgartigimod (N=22)** | **Placebo (N=9)** | **Efgartigimod (N=22)** | **Placebo (N=9)** |
| clinESSDAI Total Score | | | | |
| *Week 24* | | | | |
| n | 19 | 7 | 19 | 7 |
| Mean (S.D.) | 5.7 (6.18) | 5.3 (4.79) | **-8.1 (5.31)** | **-9.1 (7.52)** |
| S.E. | 1.42 | 1.81 | 1.22 | 2.84 |
| 95% C.I. | (2.76, 8.72) | (0.86, 9.71) | (-10.61, -5.49) | (-16.09, -2.19) |
| Median | 3.0 | 6.0 | -7.0 | -4.0 |
| Q1, Q3 | 2.0, 9.0 | 0.0, 7.0 | -12.0, -3.0 | -17.0, -3.0 |
| Min, Max | 0, 23 | 0, 14 | -17, 0 | -21, -3 |

**[00339]** *ESSDAI*

**[00340]** ESSDAI results at week 24 are shown in Table S13. A higher percentage of responders was seen in the efgartigimod group (72.7%) versus the placebo group (55.6%) based on an improvement in ESSDAI of ≥3 points at week 24.

**Table S13. ESSDAI Results**

| | Actual Values | | Change from Baseline | |
|---|---|---|---|---|
| **Domain / Visit** | **Efgartigimod (N=22)** | **Placebo (N=9)** | **Efgartigimod (N=22)** | **Placebo (N=9)** |
| ESSDAI Total Score | | | | |
| *Baseline* | | | | |
| n | 22 | 9 | | |
| Mean (S.D.) | 13.0 (5.77) | 14.6 (8.62) | | |
| S.E. | 1.23 | 2.87 | | |
| 95% C.I. | (10.40, 15.51) | (7.93, 21.18) | | |
| Median | 12.0 | 15.0 | | |
| Q1, Q3 | 8.0, 15.0 | 8.0, 18.0 | | |
| Min, Max | 6, 27 | 6, 33 | | |
| *Week 24* | | | | |
| n | 19 | 7 | 19 | 7 |
| Mean (S.D.) | 5.6 (5.44) | 5.7 (4.50) | **-6.9 (4.54)** | **-7.1 (6.84)** |
| S.E. | 1.25 | 1.70 | 1.04 | 2.59 |

| | | | | |
|---|---|---|---|---|
| 95% C.I. | (2.96, 8.20) | (1.55, 9.87) | (-9.09, -4.70) | (-13.47, -0.82) |
| Median | 3.0 | 5.0 | -5.0 | -4.0 |
| Q1, Q3 | 2.0, 9.0 | 2.0, 8.0 | -10.0, -4.0 | -13.0, -1.0 |
| Min, Max | 0, 22 | 0, 14 | -16, 0 | -19, -1 |

**[00341]** *Tear Gland Function*

**[00342]** Mean change from baseline (+/- SE) as measured by Schirmer's test is shown in FIG. 1A. Individual responses are shown in FIGs. 1B-1C.

**[00343]** Mean change from baseline (+/- SE) as measured by OSS is shown in FIG. 2A. Individual responses are shown in FIGs. 2B-2C.

**[00344]** *Salivary Gland Function*

**[00345]** Mean change from baseline in UWSF rate in mL/min (+/- SE) is shown in FIG. 3A. Individual responses are shown in FIGs. 3B-3C.

**[00346]** Mean change from baseline as measured by SGUS (Hocevar score) (+/- SE) is shown in FIG. 4. Values are provided below in Table S14.

**Table S14. Hocevar Score Results**

| | | | Change from baseline | |
|---|---|---|---|---|
| Characteristic | Efgartigimod (N=22) | Placebo (N=9) | Efgartigimod (N=22) | Placebo (N=9) |
| **Baseline (n)** | | | | |
| Mean | 24.5 | 26.8 | | |
| S.E. | 2.99 | 5.17 | | |
| **Week 16 (n)** | | | | |
| Mean | 24.0 | 29.8 | -0.4 | -0.8 |
| S.E. | 3.05 | 5.00 | 0.80 | 1.49 |
| **Week 24 (n)** | | | | |
| Mean | 21.6 | 30.9 | **-2.8** | **0.2** |
| S.E. | 3.55 | 4.32 | 0.79 | 1.20 |

**[00347]** *ESSPRI/PGA*

**[00348]** ESSPRI total score values are provided below in Table S15. PGA scores are shown in FIG. 8.

**[00349]** **Table S15. ESSPRI Score Results**

| Characteristic | Efgartigimod (N=22) | Placebo (N=9) | Change from baseline: Efgartigimod (N=22) | Change from baseline: Placebo (N=9) |
|---|---|---|---|---|
| **Baseline (n)** | *19* | *7* | | |
| Mean | 6.51 | 5.57 | | |
| S.E. | 0.29 | 0.36 | | |
| **Week 16 (n)** | *21* | *7* | *19* | *6* |
| Mean | 5.91 | 5.05 | **-0.51** | **-1.22** |
| S.E. | 0.44 | 0.73 | 0.40 | 0.56 |
| **Week 24 (n)** | *17* | *7* | *16* | *6* |
| Mean | 5.57 | 5.71 | **-0.67** | **-0.33** |
| S.E. | 0.41 | 0.58 | 0.39 | 0.62 |

**[00350]** *IgG/RF/Autoantibodies/Immune Complexes*

**[00351]** The effect of efgartigimod on serum IgG and serum RF levels is shown in Table S16. Serum RF levels, actual and percent change from baseline (mean ± SE) are also shown in FIGs. 5A and 5B, respectively. The percent change from baseline in serum IgG levels and anti-Ro52/SS-A is shown in FIG. 6B. Serum levels of anti-Ro52/SS-A, anti-Ro60/SS-A, and anti-La/SS-B are shown in FIGs. 6A, 6C, and 6D. Circulating C1q immune complex levels are shown in FIG. 7. Treatment with efgartigimod showed consistent reduction of pSS related autoantibody levels and levels of C1Q immunocomplexes.

**Table S16. Serum IgG and Serum RF levels**

| | Efgartigimod | | | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low IgG <16g/L | | High IgG >16g/L | | Rheumatoid Factor | | Low IgG <16g/L | | High IgG >16g/L | | Rheumatoid Factor | |
| | Mean (+/-SD) | % Change | Mean (+/-SD) | %Change | Mean (+/-SD) | %Change | Mean (+/-SD) | %Change | Mean (+/-SD) | %Change | Mean (+/-SD) | %Change |
| **Baseline** | 12.16 (2.712) | | 23.61 (7.49) | | 58.22 (79.64) | | 11.36 (2.5442) | | 20.02 (3.39) | | 93.27 (111.78) | |
| **Week 4** | 4.68 (2.15) | -61.65 | 10.70 (5.12) | -55.93 | 53.58 (84.38) | -17.34 | 9.75 (0.2516) | 2.29 | 18.26 (1.29) | -3.52 | 101.29 (131.42) | -4.17 |
| **Week 16** | 6.92 (8.29) | -39.24 | 11.62 (6.49) | -51.86 | 51.14 (80.41) | -16.67 | 9.98 (0.4531) | 4.87 | 18.83 (1.77) | -0.35 | 89.57 (119.62) | -7.94 |
| **Week 24** | 4.40 (1.61) | -62.66 | 11.77 (6.76) | -52.68 | 55.60 (95.86) | -19.64 | 9.72 (0.39) | 1.91 | 18.74 (2.25) | -0.94 | 96.57 (124.52) | -6.26 |

**[00353]** *Ad Hoc Analysis*

**[00354]** Clinician responder analysis of the totality of the clinical efficacy assessments available in the study participant profiles was investigated. This analysis was mostly based on improvement of systematic disease. Four clinicians independently defined each participant as a responder or non-responder, with a focus on clinical improvements and participants feeling better with or without glandular improvements. Partial responders based on medical input were assessed as a responder. The clinician responder analyses aligned strongly with STAR response (Δ22%), and moderately with CRESS response (Δ34%). The average effect of efgartigimod as assessed by clinicians was Δ29% (clinician 1: Δ26%; clinician 2: Δ26%; clinician 3: Δ30%; clinician 4: Δ35%).

**[00355]** *Adverse Events*

**[00356]** An overview of adverse events is provided in Table S17. Overall, efgartigimod was safe and well-tolerated during the study. More infections were seen in the treatment arm but all were non-serious, mild/moderate, and did not lead to treatment discontinuation.

**Table S17. Overview of Adverse Events**

| | **Efgartigimod (N=23, PYFU=12.62)** | | **Placebo (N=11, PYFU=5)** | | **Difference in TEAE rates** | |
|---|---|---|---|---|---|---|
| **Number of Participants with:** | **n (%)** | **m (ER)** | **n (%)** | **m (ER)** | **% Diff** | **(95% CI)** |
| ≥1 TEAE | 20 (87.0) | *80 (634.1)* | *7 (63.6)* | 23 (460.1) | 23.3 | *(-6.0, 54.9)* |
| ≥1 Serious TEAE | *1 (4.3)* | *1 (7.9)* | *0* | *0* | *NE* | *NE* |
| ≥1 TEAE with Grade ≥3 | *0* | 0 | *0* | *0* | *NE* | *NE* |
| ≥1 Fatal TEAE | *0* | *0* | *0* | *0* | *NE* | *NE* |
| ≥1 Treatment related TEAE according to PI | *10 (43.5)* | *21 (166.5)* | *2 (18.2)* | *3 (60.0)* | *25.3* | *(-10.4, 51.8)* |
| ≥1 Study Procedure-related TEAE | *0* | *0* | *0* | *0* | *NE* | *NE* |
| ≥1 Serious Treatment related TEAE | *0* | *0* | *0* | *0* | *NE* | *NE* |
| ≥1 TEAE for which IMP was Interrupted | *9 (39.1)* | *12 (95.1)* | *4 (36.4)* | *6 (120.0)* | *2.8* | *(-33.7, 34.6)* |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥1 TEAE for which IMP was discontinued | *1 (65.2)* | *1 (7.9)* | *0* | *0* | *NE* | *NE* |
| ≥1 TEAE of special interest | *15 (65.2)* | 25 (198.2) | *5 (45.5)* | *7 (140.0)* | 19.8 | *(-15.2, 51.4)* |
| ≥1 IRR | *6 (26.1)* | 10 (79.3) | *2 (18.2)* | *2 (40.0)* | 7.9 | *(-27.1, 34.6)* |

**[00357]** *Conclusion*

**[00358]** A treatment effect was observed on the Primary Endpoint (CRESS; Δ34%) with 45% of participants achieving CRESS response in the efgartigimod group vs 11% of participants achieving CRESS response in the placebo group. An increased response was observed in 4 out of the 5 CRESS components (ClinESSDAI, tear gland response, salivary gland response, and serology) in the efgartigimod group versus the placebo group. There was no difference between the efgartigimod group on patient reported outcome (ESSPRI).

**[00359]** A treatment effect was observed on STAR (Δ22%). ClinESSDAI showed no numeric trend in favor of efgartigimod. The effect may be masked due to small number of participants, high baseline variability and a change from baseline detectable in both efgartigimod and placebo groups. However, a consistent stepwise improvement was shown in efgartigimod arm over time.

**[00360]** Efgartigimod was safe and well tolerated, with no new safety findings reported. Efgartigimod reduced serum IgG levels over time, consistent with other programs.

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**[00361]** The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

## Claims

1. A method of treating primary Sjögren's syndrome (pSS) in a subject in need thereof, the method comprising administering to the subject an effective amount of a human neonatal Fc receptor (FcRn) antagonist, wherein the FcRn antagonist comprises or consists of a variant IgG Fc region, or FcRn-binding fragment thereof, wherein the variant IgG Fc region, or FcRn-binding fragment thereof, comprises or consists of a first Fc domain and a second Fc domain which form a homodimer or a heterodimer, and wherein the first Fc domain and the second Fc domain each comprise amino acids Y, T, E, K, F, and Y at EU positions 252, 254, 256, 433, 434, and 436, respectively and achieving a clinically established result.

2. The method of claim 1, wherein the first Fc domain and/or the second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4.

3. The method of claim 1 or 2, wherein the first Fc domain and the second Fc domain comprise an amino acid sequence independently selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4.

4. The method of any one of claims 1-3, wherein the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 1.

5. The method of any one of claims 1-3, wherein the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 2.

6. The method of any one of claims 1-3, wherein the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 3.

7. The method of any one of claims 1-3, wherein the first Fc domain and the second Fc domain comprise or consist of the amino acid sequence set forth in SEQ ID NO: 4.

8. The method of claim 1, wherein the FcRn antagonist is a population of FcRn antagonist molecules, wherein each FcRn antagonist molecule in the population consists of a dimer of a first Fc domain and a second Fc domain, and wherein the population comprises:

(a) a first subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the first subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3; and

(b) at least one of:

(i) a second subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the second subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 12, respectively;

(ii) a third subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the third subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 9, respectively;

(iii) a fourth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the fourth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3, and wherein two asparagine residues in each FcRn antagonist molecule in the fourth subpopulation are deaminated;

(iv) a fifth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the fifth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 9, respectively, and wherein one asparagine residue in each FcRn antagonist molecule in the fifth subpopulation is deaminated;

(v) a sixth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the sixth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively;

(vi) a seventh subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the seventh

subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the seventh subpopulation is oxidized;

(vii) an eighth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the eighth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 2;

(viii) a ninth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the ninth subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 2 and SEQ ID NO: 3, respectively, and wherein one methionine residue or one tryptophan residue in each FcRn antagonist molecule in the ninth subpopulation is oxidized;

(ix) a tenth subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of both the first and the second Fc domains of the FcRn antagonist molecules in the tenth subpopulation consist of the amino acid sequence set forth in SEQ ID NO: 3, and wherein two amino acid residues, independently selected from a methionine residue and a tryptophan residue, in each FcRn antagonist molecule in the tenth subpopulation is oxidized; and

(x) an eleventh subpopulation of FcRn antagonist molecules, wherein the amino acid sequences of the first and the second Fc domains of the FcRn antagonist molecules in the eleventh subpopulation consist of the amino acid sequences set forth in SEQ ID NO: 3 and SEQ ID NO: 6, respectively.

9. The method of claim 1, wherein the FcRn antagonist is efgartigimod, or a biosimilar version thereof.

10. The method of any one of claims 1-9, wherein the FcRn antagonist is administered intravenously at a dose of 10 mg/kg once weekly or once every two weeks.

11. The method of any one of claims 1-10, wherein the FcRn antagonist is administered intravenously at a dose of 10 mg/kg once weekly.

12. The method of any one of claims 1-11, wherein the FcRn antagonist is administered for 24 weeks or less.

13. The method of any one of claims 1-12, wherein the FcRn antagonist is administered once weekly for 24 weeks.

14. The method of any one of claims 1-13, further comprising administering to the subject an effective amount of one or more of a corticosteroid, a disease-modifying anti-rheumatic drug (DMARD), a non-steroidal anti-inflammatory agent, or a non-steroidal anti-rheumatic agent.

15. The method of claim 14, wherein the corticosteroid is an oral corticosteroid administered to the subject at a dose of ≤10 mg/day.

16. The method of clam 14, wherein the DMARD is selected from the group consisting of hydroxychloroquine, chloroquine phosphate, methotrexate, azathioprine, and mycophenolate mofetil.

17. The method of any one of claims 1-16, wherein the subject met the ACR-EULAR classification ≤7 years before administration of the FcRn antagonist.

18. The method of any one of claims 1-17, wherein the subject has at least a moderate level of systemic disease activity before administration of the FcRn antagonist.

19. The method of any one of claims 1-18, wherein the subject has a EULAR Sjögren's syndrome disease activity index (ESSDAI) score of ≥5 before administration of the FcRn antagonist.

20. The method of any one of claims 1-19, wherein the subject has a detectable serum level of a pSS-related autoantibody before administration of the FcRn antagonist.

21. The method of any one of claims 1-20, wherein the subject has a detectable serum level of an anti-Ro/SS-A antibody and an anti-La/SS-B antibody before administration of the FcRn antagonist.

22. The method of any one of claims 1-21, wherein the subject has an unstimulated whole salivary flow (UWSF) rate >0 and/or a stimulated whole salivary flow (SWSF) rate >0.10 before administration of the FcRn antagonist.

23. The method of any one of claims 1-22, wherein the subject shows three or more clinically established results following administration of the FcRn antagonist, wherein the clinically established results are selected from the group consisting of:

a) a clinical ESSDAI (clinESSDAI) score of <5 points;
b) a decrease in EULAR Sjögren's syndrome patient reported index (ESSPRI) score of ≥1 point or ≥15%, compared to a baseline value;
c) an increase in tear gland function;
d) an increase in salivary gland function; and
e) a decrease in serum rheumatoid factor (RF) of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value.

24. The method of any one of claims 1-23, wherein the subject shows:

a) a clinESSDAI score of <5 points;
b) an increase in tear gland function;
c) an increase in salivary gland function; and
d) a decrease in serum RF of at least 25%, compared to a baseline value, or a decrease in serum IgG of at least 10%, compared to a baseline value;

following administration of the FcRn antagonist.

25. The method of claim 23 or 24, wherein the increase in tear gland function is measured by Schirmer's test and/or ocular staining score (OSS), wherein

- if the subject shows a baseline value of ≤5 mm as measured by Schirmer's test, a response is defined as an increase of at least 5 mm from the baseline value; or

- if the subject shows a baseline value of ≥3 points as measured by OSS, a response is defined as a decrease of at least 2 points from the baseline value; or
- if the subject shows a baseline value of > 5 mm as measured by Schirmer's test and shows a baseline value of < 3 points as measured by OSS, a response is defined as no change that results in an abnormal OSS or Schirmer's score.

26. The method of claim 23 or 24, wherein the increase in salivary gland function is measured by UWSF and/or salivary gland ultrasonography (SGUS), wherein a response is defined as:

- an increase in UWSF of at least 25%, compared to a baseline value if the baseline value is > 0 mL/min, or any increase in UWSF if the baseline value is 0 mL/min; or
- a decrease in Hocevar score as measured by SGUS of at least 25%, compared to a baseline value.

27. The method of any one of claims 23-26, wherein the responses are measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

28. The method of any one of claims 1-27, wherein the subject shows a decrease in ESSDAI score and/or clinESSDAI score following administration of the FcRn antagonist, compared to a baseline value.

29. The method of claim 28, wherein the ESSDAI score and/or the clinESSDAI score is measured following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

30. The method of claim 28 or 29, wherein the subject shows a decrease of at least 5 points in the ESSDAI score and/or the clinESSDAI score, following administration of the FcRn antagonist.

31. The method of any one of claims 28-30, wherein the subject has an ESSDAI score of <5 and/or a clinESSDAI score of <5, following administration of the FcRn antagonist.

32. The method of any one of claims 1-31, wherein the subject shows an increase in Sjögren's Tool for Assessing Response (STAR) score following administration of the FcRn antagonist, compared to a baseline value.

33. The method of claim 32, wherein the STAR score is measured following administration of the FcRn antagonist once weekly for 24 weeks.

34. The method of claim 32 or 33, wherein the subject has a STAR score of ≥5 following administration of the FcRn antagonist.

35. The method of any one of claims 1-34, wherein the subject shows a change in SWSF rate, UWSF rate, Hocevar score, Schirmer's test score, and/or OSS, following administration of the FcRn antagonist, compared to a baseline value.

36. The method of claim 35, wherein the SWSF rate, the UWSF rate, the Hocevar score, the Schirmer's test score, and/or the OSS is measured at following administration of the FcRn antagonist once weekly for 16 or 24 weeks.

37. The method of any one of claims 1-36, wherein the subject shows a reduction in a serum level of total IgG, RF, an autoantibody, or an immune complex following administration of the FcRn antagonist, compared to a baseline value.

38. The method of claim 37, wherein the serum level of total IgG, RF, an autoantibody, or an immune complex is measured following administration of the FcRn antagonist once weekly for 4, 16, or 24 weeks.

39. The method of claim 37 or 38, wherein the immune complex is a C1q immune complex.

40. The method of claim 37 or 38, wherein the autoantibody is an anti-Ro52/SS-A antibody, an anti-Ro60/SS-A antibody, or an anti-La/SS-B antibody.

41. An FcRn antagonist for use in the treatment of pSS, wherein the treatment is performed according to the method of any one of claims 1-40 and the treatment induces a CRESS score of at least 45% in subjects.

42. An FcRn antagonist for use in the manufacture of a medicament for the treatment of pSS, wherein the treatment is performed according to the method of any one of claims 1-40.

43. Use of an FcRn antagonist for the treatment of pSS according to the method of any one of claims 1-40.

44. Use of an FcRn antagonist for the manufacture of a medicament for treatment of pSS, wherein the treatment is performed according to the method of any one of claims 1-40.

45. The method of any one of claims 1- 22, wherein said subject has a CRESS response of at least 45% when treated with efgartigimod when tested at 24 weeks following initial treatment with efgartigimod.