TITLE PAGE

Protocol Title:

A Phase 3, Randomized, Open-Label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis

Protocol Number: ARGX-113-2001

Amendment Number: 1

Compound: Efgartigimod

Brief Title: Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis

Study Phase: 3

Acronym: ADAPT^{SC}

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DOCUMENT HISTORY

Document	Date
Amendment 1	02 Jul 2021
Original Protocol	15 Oct 2020

Amendment 1 (02 Jul 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Increase sample size from 46-76 participants to approximately 110 participants. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Drug Safety Reporting	Updated information: Email: [redacted] Toll-free Fax: [redacted]	The email address and fax number for drug safety reporting have been updated.
1.1 Synopsis 9.2 Sample Size Determination	Increase sample size to approximately 110 participants	Although 76 participants would provide enough data to establish non-inferiority between SC and IV formulations based on IgG reduction at day 29, the increase in sample size to approximately 110 participants will allow better quantification of the clinical safety and efficacy profile of the SC formulation in patients with gMG while the IV formulation will serve as a reference treatment in this randomized study.
2.3.1 Efgartigimod Risk Assessment Section 11 References	Updated text: Participants who are women of childbearing potential (WOCBP) must use highly effective or acceptable method of contraception (see inclusion criterion 8 and Section 10.5)	The potential risk to teratogenicity/fetotoxicity mitigation strategy was updated to align with the current Investigator's Brochure (IB) (IB version 9.0). However, in this protocol amendment, the contraception requirements are unchanged from the original protocol dated 15 Oct 2020. Additionally, the IB reference was updated to reflect the current version.
6.8.3 Prohibited Medication and Procedures	Updated text: PLEX, Ig therapy (IVIg and SCIg), immunoadsorption, or a change in	The text was updated for alignment throughout the protocol because any type of immunoglobulin therapy, regardless

Section # and Name	Description of Change	Brief Rationale
	dosage or type of corticosteroid are considered rescue therapy if both of the following conditions apply:	of the formulation, is considered rescue therapy.
8.2.6 Clinical Safety Laboratory Assessments	Updated text: The actual sample collection date and time must be collected in the participant's source document and included in the central laboratory data transfer.	As the sample collection date and time is already collected on the central lab requisition forms and loaded into the database from the lab data transfer, there is no need to collect this data on the laboratory assessment eCRF page in duplicate
10.1.3 Informed Consent Process	Updated text: Prior to signing the ICF, the study participants will be instructed not to participate in any other clinical study that involves a therapeutic intervention until the completion of the study.	It is not required to exclude or discontinue participants who are participating in a study that does not involve another intervention because this does not constitute a safety concern for participants.
10.4.2 Definition of SAE	Removed text: An SAE is defined as any untoward medical occurrence that, at any dose: ~~Is a suspected transmission of any infectious agent via an authorized medicinal product~~	This item does not need to be considered an SAE in this study, and as such this item must be disregarded.
10.7.3.5 Mandatory Site Visits and Home Visits	Removed text: ~~If needed, all of the previously listed visits can be performed by a home nurse except the screening visit.~~	Home nurse services are not a part of this study, so this sentence must be disregarded.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3, Randomized, Open-Label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis

Brief Title: Evaluating the Pharmacodynamic Noninferiority of Efgartigimod PH20 SC Administered Subcutaneously as Compared to Efgartigimod Administered Intravenously in Patients With Generalized Myasthenia Gravis

Rationale:

The aim of this study is to investigate the pharmacodynamics (PD), pharmacokinetics (PK), safety, tolerability, immunogenicity, and clinical efficacy of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC) (efgartigimod PH20 SC) as compared to efgartigimod intravenously (IV) infused (efgartigimod IV) in patients with generalized myasthenia gravis (gMG).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To demonstrate that the PD effect of injections of 1000 mg efgartigimod PH20 SC, administered once per week (q7d) for 4 administrations, is noninferior to that of IV infusions of efgartigimod at a dose of 10 mg/kg administered q7d for 4 administrations.	• Percent reduction from baseline in total immunoglobulin G (IgG) levels at day 29, ie, 7 days after the fourth IV or SC administration

Objectives	Endpoints
Secondary	
• To compare the PD effect of efgartigimod PH20 SC and efgartigimod IV over time	• Absolute values, change from baseline, and percent reduction from baseline in total IgG levels over time • Absolute values, change from baseline, and percent reduction from baseline in acetylcholine receptor binding autoantibodies (AChR-Ab) levels over time in AChR-Ab positive patients • Absolute values, change from baseline, and percent reduction from baseline in IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time • Area under the effect curve (AUEC) of the percentage reduction from baseline total IgG and similar AUEC for each IgG subtype per dosing interval (days 1–8, days 8–15, days 15–22, and days 22–29), days 1–29, and over the entire study (days 1–71)
• To evaluate the PK of efgartigimod PH20 SC and efgartigimod IV	• PK parameters: maximum concentration (C_{max}) (after all doses for the IV treatment arm), concentration observed predose (C_{trough})
• To evaluate the safety, tolerability, and immunogenicity of efgartigimod PH20 SC and efgartigimod IV	• Incidence and prevalence of anti-drug antibodies (ADAs) against efgartigimod • Incidence and prevalence of ADAs against rHuPH20 in the SC treatment arm • Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram (ECG) results

Objectives	Endpoints
• To evaluate the clinical efficacy of efgartigimod PH20 SC and efgartigimod IV	• Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders • Number and percentage of Quantitative Myasthenia Gravis (QMG) responders • Change from baseline in MG-ADL total score over time • Change from baseline in QMG score over time
Exploratory	
• [redacted]	[redacted]

Overall Design:

ARGX-113-2001 is a randomized, open-label, parallel-group, multicenter study in patients with generalized myasthenia gravis (gMG), including participants who are seropositive and participants who are seronegative for the acetylcholine receptor binding autoantibodies (AChR-Ab). After screening, patients will be randomized to receive either efgartigimod IV 10 mg/kg q7d for 4 infusions or efgartigimod PH20 SC 1000 mg q7d for 4 injections concomitant to their current gMG therapy. Randomization will be stratified by Japanese versus non-Japanese participants. Within non-Japanese participants, randomization will be further stratified by AChR-Ab status. Participants randomized to receive the SC injections or their caregivers will be trained in self-administration or caregiver-supported administration, respectively, and will be permitted to perform administration of the investigational medicinal product (IMP) on-site under supervision from the site staff. An independent Data Safety Monitoring Board (DSMB) will periodically review and evaluate the accumulated study data for participant safety, study conduct, and study progress. The DSMB will make recommendations to the sponsor concerning the continuation, modification, or termination of the study.

Brief Summary:

The purpose of this study is to investigate the PD, PK, safety, tolerability, immunogenicity, and clinical efficacy of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) as compared to efgartigimod IV infused in patients with gMG to evaluate the PD noninferiority of the SC formulation compared to the intravenous formulation. Study details include:

Study Duration: 12 weeks

Treatment Duration: 3 weeks

Health Measurements: Total levels of immunoglobulin G (IgG), levels of IgG subtypes, AChR-Ab levels, MG-ADL, QMG

Visit Frequency: Every week through visit 9, followed by a 2-week period between visit 9 and the end of the study visit

Number of Participants:

Approximately 110 participants will be enrolled and randomized in a 1:1 ratio to receive either efgartigimod PH20 SC or efgartigimod IV in addition to their concomitant gMG therapy. Approximately 110 participants are considered sufficient to allow better quantification of the safety and efficacy between the IV and SC routes of administration for efgartigimod. See also Section 9.2. Randomization will be stratified by Japanese versus non-Japanese participants. Within non-Japanese participants, randomization will be further stratified by AChR-Ab status. Up to 20% of participants included in the study will be AChR-Ab seronegative Japanese and up to 20% will be AChR-Ab seronegative non-Japanese patients.

Note: “Enrolled” means a participant, or their legally acceptable representative, has agreed to participate in a clinical study following completion of the informed consent process and screening. Potential participants screened to determine study eligibility but who do not participate in the study are not considered enrolled unless otherwise specified by the protocol. “Randomized” means that an enrolled participant has been randomly assigned to a treatment arm.

Intervention Groups and Duration:

The study duration is approximately 12 weeks, spanning the following study periods:

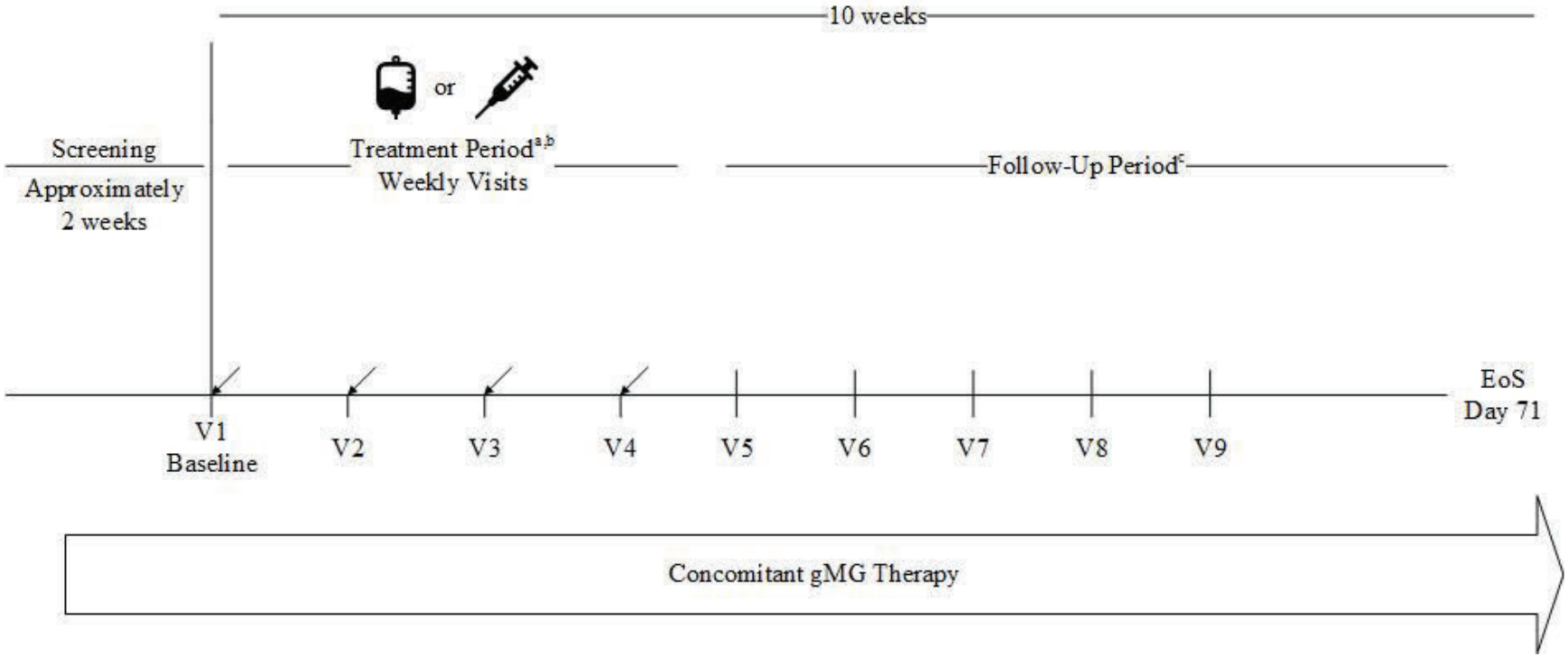
- screening period: approximately 2 weeks, with an additional 5 days allowed if needed to ensure AChR-Ab test results have been received
- treatment period: 3 weeks
- follow-up period: 7 weeks

On day 1, participants will be randomized to receive either efgartigimod IV 10 mg/kg or efgartigimod PH20 SC 1000 mg during the treatment period. All participants will receive a total of 4 administrations of the assigned IMP, administered q7d. Participants receiving efgartigimod PH20 SC 1000 mg or their caregivers will be trained to administer the IMP. Participants will be discontinued from treatment if it is in the participant’s best interest, as determined by the investigator or sponsor.

Data Monitoring/Other Board: Yes (see Section 10.1.5.1)

1.2. Schema

Figure 1: Schema for Study ARGX-113-2001



EoS=end of study; gMG=generalized myasthenia gravis; IMP=investigational medicinal product; IV=intravenous(ly); PH20=rHuPH20 (recombinant human PH20 hyaluronidase); SC=subcutaneous; V=visit

[a] Participants will be randomized in a 1:1 ratio to either the efgartigimod IV 10 mg/kg treatment arm or the efgartigimod PH20 SC 1000 mg treatment arm. Participants will receive IMP every 7 days for 4 administrations.

[b] Participants receiving efgartigimod PH20 SC or their caregivers will be trained in self-administration of the IMP. Once a participant or caregiver is considered competent to self-administer, they will be allowed to self-administer the IMP on site under supervision of the site staff starting at V2.

[c] The follow-up period consists of weekly visits through V9, followed by a 2-week period between V9 and EoS.

1.3. Schedule of Activities

Table 1: Schedule of Activities for Study ARGX-113-2001

	Screening	Treatment Period				Follow-up Period					End of Study	Unscheduled
Visit		**V1 Baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EoS[a]**	**UNS[b]**
Study Day (visit window)	**-14 to -1**	**1**	**8(±1)**	**15(±1)**	**22(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**50(±2)**	**57(±2)**	**71(±3)**	
Activity												
Informed consent[c]	X											
Inclusion/exclusion criteria	X	X										
SARS-CoV-2 test[d]	X											X
Medical/surgical history[e]	X											
Demographic data	X											
Height and weight[f]	X	X									X	X
MG-ADL	X	X	X	X	X	X	X	X	X	X	X	X
QMG[g]		X	X	X	X	X	X	X	X	X	X	X
MG-QoL15r		X									X	
EQ-5D-5L		X									X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X
SIB risk monitoring[i]	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Treatment Period				Follow-up Period					End of Study	Unscheduled
Visit		**V1 Baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EoS[a]**	**UNS[b]**
Study Day (visit window)	**-14 to -1**	**1**	**8(±1)**	**15(±1)**	**22(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**50(±2)**	**57(±2)**	**71(±3)**	
Activity												
Clinical laboratory tests[j]	X	X	X	X	X	X	X	X	X	X	X	X
AChR-Ab serotype	X											
Single 12-lead ECG[k]	X	X			X						X	X
Urinalysis	X	X			X	X					X	X
Pharmacokinetics[l]		X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamics[m]		X	X	X	X	X	X	X	X	X	X	X
Immunogenicity[n]		X		X		X			X		X	X
Pregnancy test[o]	X	X	X	X	X	X					X	X
Viral screen[p]	X											
Randomization[q]		X										
Training for self-administration of SC IMP[r]		X	X	X	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Administration of IMP[s]		X	X[t]	X[t]	X[t]							
Assessment of administration site[u]	Continuous monitoring											
Hospitalization monitoring[v]	Continuous monitoring											

	Screening	Treatment Period				Follow-up Period					End of Study	Unscheduled
Visit		**V1 Baseline**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EoS[a]**	**UNS[b]**
Study Day (visit window)	**-14 to -1**	**1**	**8(±1)**	**15(±1)**	**22(±1)**	**29(±2)**	**36(±2)**	**43(±2)**	**50(±2)**	**57(±2)**	**71(±3)**	
Activity												
Prior/concomitant therapy[v]	Continuous monitoring											
Adverse events[v]	Continuous monitoring											

Ab= antibody; AChR-Ab=acetylcholine receptor binding autoantibody; AChE=acetylcholinesterase; ADA=anti-drug antibodies; ECG=electrocardiogram; EoS=end of study; EQ-5D-5L=EuroQoL 5 Dimensions 5 Levels; ER=emergency room; FSH= follicle-stimulating hormone; ICU=intensive care unit; IgG=immunoglobulin G; IMP=investigational medicinal product; IV=intravenous; MG-ADL=Myasthenia Gravis-Activities of Daily Living total score; MGFA=Myasthenia Gravis Foundation of America; MG-QoL15r=Myasthenia Gravis Quality of Life Questionnaire (15 item scale revised); NAb=neutralizing antibody; PD=pharmacodynamics; PHQ=Patient Health Questionnaire; PK=pharmacokinetics; PR= atrioventricular node delay interval; QMG=Quantitative Myasthenia Gravis score; QRS=duration of ventricular depolarization; QT=total duration of ventricular depolarization; QTcF=rate-corrected QT intervals using Fridericia's formula; PH20= recombinant human hyaluronidase PH20 (rHuPH20); RR= time between heartbeats; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SC=subcutaneous; SIB=Suicide Ideation and Behavior; SoA=Schedule of Activities; UNS=unscheduled; V=visit

Note: All activities are performed predose on dosing days unless otherwise indicated. It is recommended to perform the MG-ADL scale prior to all other assessments.

[a] After a participant completes the study and all EoS visit activities, the participant will be allowed, if eligibility criteria are met, to roll over into the open-label extension study ARGX-113-2002 to receive efgartigimod PH20 SC 1000 mg.

[b] A UNS visit can occur at the request of the participant or the investigator. During the UNS visit, activities as indicated in the SoA can be performed at the discretion of the investigator, depending on the reason for the UNS visit.

[c] No study-related activities will be initiated before the participant signs the informed consent form.

[d] A nasopharyngeal swab will be performed to sample nasal and throat mucosal cells. Participants may be retested as needed (see Section 10.7)

[e] Medical history will also include all ER visits, hospitalizations, and ICU admissions that have occurred in the previous 12 months. All available vaccination history will be recorded. For vaccines where multiple doses or boosters are received, only the most recent must be recorded. See Section 8.2.5.

[f] Height will only be measured at screening and weight will be measured at screening, at baseline, at the EoS visit, and at UNS visits.

[g] AChE inhibitors must be withheld for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the MGFA).

[h] It is recommended that the method used to measure body temperature at screening is maintained throughout the study for each patient.

[i] The SIB Risk Monitoring assessment is based on question 9 of the PHQ. See Section 8.2.10.

[j] Blood samples for clinical laboratory (hematology/clinical chemistry and FSH, if applicable) safety assessments will be collected predose on dosing days. In addition, total IgG at screening is to be assessed for defining eligibility. Participants need to be in a fasted state (defined as no food or drink, except for water, which is allowed until at least 4 hours prior to sampling) for at least 8 hours prior to each sampling.

[k] The following ECG intervals will be measured: RR, PR, QRS, QT, and QTcF.

[l] On dosing days, PK samples will be collected predose (within 1 hour prior to start of administration) and at the end of each infusion for IV (within 1 hour after end of infusion). No postdose PK samples will be collected in case of IMP administration by SC injection.
[m] The PD analysis comprises levels of total IgG, IgG subtypes (IgG1, IgG2, IgG3 and IgG4) and levels of AChR-Abs (for AChR-Ab seropositive participants only).
[n] Titers of ADA against efgartigimod and presence of NAbs against efgartigimod will be measured in serum in both the IV and SC treatment arms. Plasma titer levels of ADA and NAbs against rHuPH20 will be measured in the SC treatment arm only.
[o] Female participants of childbearing potential will be tested for pregnancy using a serum test at screening and a urine test at all other visits.
[p] The virology screen includes relevant tests to comply with exclusion criteria 7 and is performed on samples taken at screening.
[q] Randomization will be performed after screening within approximately 2 weeks and only after confirmation of the eligibility of the patient. If the AChR-Ab test result is not available in time (ie, within the 2 weeks screening window), the screening window can be increased by a maximum of 5 calendar days as needed.
[r] Applicable to participants in the SC treatment arm only. These participants and their caregivers will be trained in self-administration of efgartigimod PH20 SC and the training can continue until the participant or their caregiver is capable of self-administration. Training sessions marked with parentheses "(X)" are optional.
[s] The IMP (efgartigimod IV or efgartigimod PH20 SC) will be administered at visits 1, 2, 3, and 4 either as an 1-hour IV infusion or an SC injection. Participants will remain at the site for at least 1 hour following the end of the drug administration to be monitored for safety.
[t] Participants randomized to the SC treatment arm or their caregivers will be allowed to administer efgartigimod PH20 SC at the site under supervision if the self-administration/caregiver-supported administration training is completed and documented and if the site staff determine that the participant is ready to do so.
[u] The assessment of the administration site will be performed prior to dosing and 1 hour postdose on dosing days, in addition to continuous monitoring by the participant in between visits.
[v] Adverse events, use of concomitant therapies, use of rescue therapy, medical procedures performed on the participants, and hospitalizations will be collected from the time the informed consent form is signed until the last study-related activity. Relevant prior therapy and all available vaccination history will only be collected at screening. See Section 6.8 and Section 8.3.

2. INTRODUCTION

Efgartigimod is a human immunoglobulin (Ig) G1 (IgG1)-derived Fc fragment that binds with nanomolar affinity to human FcRn that is being developed for the treatment of generalized myasthenia gravis.

2.1. Study Rationale

The aim of this study is to investigate the pharmacodynamics (PD), pharmacokinetics (PK), safety, tolerability, immunogenicity, and clinical efficacy of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20, brand name Hylenex®) administered subcutaneously (SC) (efgartigimod PH20 SC) as compared to efgartigimod intravenously (IV) infused (efgartigimod IV) in patients with generalized myasthenia gravis (gMG).

The PD of efgartigimod IV at 10 mg/kg and efgartigimod PH20 SC at a fixed dose of 1000 mg will be evaluated, as per the primary objective. The SC formulation of efgartigimod will include rHuPH20 because the enzyme allows manual SC injection within a few minutes and using larger volumes than what is possible without rHuPH20.

2.2. Background

gMG is a rare, chronic, neuromuscular autoimmune disease caused by pathogenic IgGs targeting the neuromuscular junction (NMJ), producing reduced neuromuscular transmission and debilitating and potentially life-threatening muscle weakness and chronic fatigue. Generalized muscle weakness results in difficulties in mobility, speech, swallowing, vision, and respiration. Up to 20% of patients develop potentially life-threatening myasthenic crisis involving respiratory failure requiring mechanical ventilation.[1,2]

ARGX-113 (efgartigimod) is an investigational antibody fragment and a first-in-class neonatal Fc receptor (FcRn) antagonist that is being evaluated for the treatment of patients with severe autoimmune diseases mediated by pathogenic IgG autoantibodies, including gMG. Approximately 90% of patients with gMG have detectable levels of IgG autoantibodies in the serum. Most commonly, these antibodies are against the acetylcholine receptor (AChR).[3] Efgartigimod leads to degradation circulating disease-causing pathogenic antibodies by blocking FcRn.

FcRn is present throughout life and expressed predominantly in endothelial cells and cells of myeloid lineage. FcRn has a specific role in IgG homeostasis, recycling all IgG subtypes, which rescues them from lysosomal degradation. This FcRn-mediated recycling results in the longer half-life and higher concentrations of IgG, including pathogenic IgG autoantibodies, as compared to other Igs that are not recycled by FcRn. FcRn also promotes transcytosis of IgG into tissues. Additionally, FcRn recycles albumin using a site that is distinct from the IgG binding site.

Efgartigimod is a human IgG1 antibody Fc fragment, a natural ligand of FcRn, engineered for increased FcRn affinity at both physiological and acidic pH. Efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated recycling of IgGs and increasing IgG degradation.

In the phase 3 study ARGX-113-1704 in patients with gMG, treatment with efgartigimod IV resulted in a statistically significant increase in the percentage of participants responding to treatment based on the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score and the Quantitative Myasthenia Gravis (QMG) score as compared to placebo. Additionally, efgartigimod IV treatment resulted in a substantial mean percent decrease in total IgG levels as compared to no observable change in participants who received placebo, which further supported the results of the phase 2 study ARGX-113-1602.

The efgartigimod PH20 SC formulation was tested in healthy subjects in study ARGX-113-1901, which resulted in a dose-dependent decrease in total IgG levels.

A detailed description of the chemistry, pharmacology, efficacy, and safety of efgartigimod is provided in the Investigator's Brochure (IB). For more information on rHuPH20, refer to the IB for rHuPH20.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of efgartigimod may be found in the IBs for efgartigimod[4] and rHuPH20[5].

2.3.1. Efgartigimod Risk Assessment

Overall, efgartigimod IV has been well tolerated in healthy participants subjects as well as in patients with gMG. Efgartigimod PH20 SC was well tolerated in healthy participants. No major safety findings have arisen in ongoing and completed studies with either formulation of efgartigimod. Further information can be found in the IB[4].

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
Immune modulation leading to increased infection risk	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the infection risk. However, no opportunistic infection with efgartigimod has been observed. Efgartigimod treatment may be associated with a small increase in the frequency of infections. However, the type and severity of these infections are not different to those which patients with gMG are ordinarily susceptible. There is no increase in the type of infectious events that might be expected from high degrees of immunosuppression	Participants with clinically significant uncontrolled infections, malignancies, recent surgeries, and/or the presence of certain viral infections are excluded (see Section 5.2). Administration of efgartigimod to a participant will be interrupted if a clinically significant infection occurs. Infections are considered an adverse event of special interest (AESI) and a detailed questionnaire will be completed for any infectious events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
	(eg, tuberculosis or opportunistic infections).	
Injection and/or infusion-related reactions (IRRs)	All therapeutic proteins have the potential to elicit antibody or other immune or nonimmune mediated responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. None of the participants treated with either efgartigimod formulation had a treatment-emergent adverse event (TEAE) that was a drug hypersensitivity or anaphylactic reaction	Participants will be monitored at the site for 1 hour after administration and administration site reactions will be monitored continuously (see Section 1.3).
Potential risk to teratogenicity/fetotoxicity	No clinical studies have been performed to evaluate reproductive risks. However, nonclinical studies performed suggest that there is no risk of teratogenicity or fetotoxicity.	Pregnant women are excluded. Participants who are women of childbearing potential (WOCBP) must use a highly effective or acceptable method of contraception (see inclusion criterion 8 and Section 10.5)

2.3.2. Efgartigimod Benefit Assessment

Efgartigimod has been shown to effectively reduce IgG antibodies in several clinical studies, including in healthy subjects, patients with immune thrombocytopenia (ITP), patients with pemphigus vulgaris, and patients with gMG (see the IB). Patients with gMG also saw improvements in gMG symptoms and quality of life. Studies involving patients with gMG are described in the following text.

- A phase 2 study (ARGX-113-1602) enrolled patients with gMG that were seropositive for AChR binding autoantibodies (AChR-Ab) and had an MG-ADL total score of ≥5 with more than 50% of this score attributed to nonocular items. Participants received efgartigimod IV 10 mg/kg or placebo q7d for 4 infusions.
  - Efgartigimod IV showed statistically significant improvements as compared to placebo in clinical evaluations of MG symptoms, including the MG-ADL and the QMG.
  - The efgartigimod IV treatment arm showed a substantial percent reduction from baseline in total IgG levels as compared to the placebo arm, where no discernable difference from baseline was observed.

  - Efgartigimod IV was safe and well tolerated, with all treatment-emergent adverse events (TEAEs) classified as mild or moderate.

- A phase 3 study (ARGX-113-1704) enrolled patients with gMG with an MG-ADL total score ≥5 with more than 50% of the total score coming from nonocular symptoms, regardless of AChR-Ab presence in the serum. Participants received efgartigimod IV 10 mg/kg or placebo q7d for 4 infusions, with additional treatment cycles allowed based on the clinical response of the participant as evaluated by the MG-ADL total score.
  - The efgartigimod IV treatment arm had a statistically significantly higher percentage (67.7%) of MG-ADL responders as compared to the placebo arm (29.7%) among AChR-Ab positive patients. In the overall population (AChR-Ab positive and AChR-Ab negative participants), the efgartigimod treatment arm also reported a significantly higher percentage of MG-ADL responders (67.9%) compared to the placebo arm (37.3%).
  - The efgartigimod IV treatment arm had a statistically significantly higher percentage of QMG responders (63.1%) as compared to the placebo arm (14.1%) among AChR-Ab positive participants.
  - In the AChR-Ab seropositive population, the maximum mean percent change from baseline in total IgG levels was approximately 61% 1 week after the last infusion of a treatment cycle. No substantial mean percent change in total IgG levels from baseline was observed in the placebo arm. The results were comparable between AChR-Ab seropositive participants and the overall population.
  - Efgartigimod IV 10 mg/kg q7d was safe and well tolerated. The efgartigimod IV arm had a lower percentage of participants reporting TEAEs than the placebo arm. The majority of TEAEs reported were mild or moderate in severity.

2.3.3. rHuPH20 Risk Assessment

More information on the use of rHuPH20 (brand name Hylenex) is available in the rHuPH20 IB[5].

SC injections were well tolerated in healthy subjects, dehydrated pediatric patients, hospice and palliative care patients, patients with type 1 and 2 diabetes, and patients with rheumatoid arthritis. SC injections of rHuPH20 alone or in combination with lactated Ringer's solution, normal saline, co-injected drugs (eg, morphine, ceftriaxone, ondansetron), peptides (eg, insulin and insulin analogs), or proteins (IgG and adalimumab) have been well tolerated in all clinical studies.

Most AEs observed were mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions, which occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also reported.

Hylenex prescribing information as of February 2016 contains the following warnings and precautions:

- rHuPH20 should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. rHuPH20 should not be used to reduce the swelling of bites or stings.
- rHuPH20 should not be applied directly to the cornea. It is not for topical use.

2.3.4. rHuPH20 Benefit Assessment

rHuPH20 locally degrades hyaluronan under physiological conditions, acting as a permeation enhancer in the SC space. rHuPH20 activity allows for increased dispersion and absorption of coadministered therapies and facilitates the delivery of larger volumes in rapid SC injections with limited swelling, induration, or pain. rHuPH20 may enhance the dispersion and absorption of efgartigimod, allowing an SC injection to achieve the target exposure, PD effect, and associated clinical benefit. This formulation and SC administration are expected to improve patient convenience as compared to the IV formulation, as participants or their caregivers will be permitted to administer efgartigimod PH20 SC once they are competent to do so.

2.3.5. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with efgartigimod and rHuPH20 are justified by the anticipated benefits that may be afforded to participants with gMG.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate that the PD effect of injections of 1000 mg efgartigimod PH20 SC, administered once per week (q7d) for 4 administrations, is noninferior to that of IV infusions of efgartigimod at a dose of 10 mg/kg administered q7d for 4 administrations.	• Percent reduction from baseline in total IgG levels at day 29, ie, 7 days after the fourth IV or SC administration
Secondary	
• To compare the PD effect of efgartigimod PH20 SC and efgartigimod IV over time	• Absolute values, change from baseline and percent reduction from baseline in total immunoglobulin (IgG) levels over time • Absolute values, change from baseline and percent reduction from baseline in AChR-Ab levels over time in AChR- Ab positive patients • Absolute values, change from baseline, and percent reduction from baseline in IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time • Area under the effect curve (AUEC) of the percentage reduction from baseline total IgG and similar AUEC for each IgG subtype per dosing interval (days 1–8, days 8–15, days 15–22, and days 22–29), days 1–29, and over the entire study (days 1–71)
• To evaluate the PK of efgartigimod PH20 SC and efgartigimod IV	• PK parameters: maximum concentration (C_{max}) (after all doses for the IV treatment arm), concentration observed predose (C_{trough})

Objectives	Endpoints
• To evaluate the safety, tolerability, and immunogenicity of efgartigimod PH20 SC and efgartigimod IV	• Incidence and prevalence of anti-drug antibodies (ADAs) against efgartigimod • Incidence and prevalence of ADAs against rHuPH20 in the SC treatment arm • Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram (ECG) results
• To evaluate the clinical efficacy of efgartigimod PH20 SC and efgartigimod IV	• Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders • Numbers and percentage of QMG responders • Change from baseline in MG-ADL total score over time • Change from baseline in QMG score over time
Exploratory	
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

- This is a phase 3, multicenter, randomized, open-label, parallel-group study to evaluate the noninferiority of the PD effect of efgartigimod PH20 SC 1000 mg as compared to efgartigimod IV 10 mg/kg in patients with gMG. The safety, clinical efficacy, immunogenicity, PK of efgartigimod PH20 SC 1000 mg and efgartigimod IV 10 mg/kg will also be assessed.
- The total study duration is approximately 12 weeks:
    - approximately 2 weeks of screening, with an additional 5 days allowed as needed to ensure AChR-Ab test results have been received
    - 3 weeks of treatment
    - 7 weeks of follow-up
- The primary target population is adult patients with generalized myasthenia gravis (gMG), who have an MG-ADL total score ≥5 points and greater than 50% of the total score attributed to nonocular symptoms, at screening and baseline. Participants must be receiving a stable dose of concomitant treatment for gMG.
- Serum from participants will be tested to determine their AChR-Ab status. Up to 20% of the participants randomized can be seronegative for AChR-Abs in both the overall population and the Japanese participant population.
- Randomization will be stratified by Japanese versus non-Japanese participants. Within non-Japanese participants, randomization will be further stratified by AChR-Ab status.
- After confirmation of eligibility, participants will be randomized 1:1 at the day 1 visit to receive efgartigimod IV 10 mg/kg or efgartigimod PH20 SC 1000 mg every 7 days (q7d) for 4 administrations.
- Efgartigimod IV will be administered by a 1-hour IV infusion performed by the site staff.
- Efgartigimod PH20 SC will be administered by injection into the abdominal subcutaneous tissue. Participants receiving efgartigimod PH20 SC or their caregivers will be trained in self-administration or caregiver-supported administration of the IMP. If the participant or the caregiver successfully completes the training to the satisfaction of the investigator and the participant, the participant or the caregiver may administer the second, third and/or fourth injections at the site under supervision.
- At End of Study (EoS), eligible participants will be offered the option to roll over into a single-arm extension study ARGX-113-2002 to receive efgartigimod PH20 SC. Participants who complete this study may be eligible to participate in the extension study.

4.2. Scientific Rationale for Study Design

The aim of this study is to assess the PD, PK, safety, tolerability, immunogenicity, and clinical efficacy of efgartigimod coadministered with rHuPH20 subcutaneously (efgartigimod PH20 SC) as compared to efgartigimod IV in patients with gMG. IgG autoantibodies lead to gMG

symptoms, resulting from destruction of important molecules in the NMJ, including AChR. IgG antibody total levels, levels of IgG subtypes (IgG1, IgG2, IgG3, and IgG4), and levels of AChR-Abs will be evaluated as an objective surrogate measure for gMG treatment efficacy, as study ARGX-113-1704 showed that reduction total IgG levels and AChR-Ab levels (in AChR-Ab seropositive participants) correlate with reductions in the MG-ADL total score. Clinical efficacy will be measured by the MG-ADL total score and the QMG score, which are well-established measures for assessing disease severity.

The PD of efgartigimod IV at 10 mg/kg and efgartigimod PH20 SC at a fixed dose of 1000 mg will be compared, as per the primary objective of this study (see Section 3). The SC formulation of efgartigimod will include rHuPH20 because the enzyme facilitates the SC delivery of volumes greater than ~2 mL and may increase the absorption and dispersion of efgartigimod. rHuPH20 has been approved in the United States as Hylenex recombinant as a permeation enhancer for SC delivery of fluid for achieving hydration and as an adjuvant to increase the dispersion and absorption of other injected drugs. rHuPH20 depolymerizes hyaluronan under physiologic conditions, allowing for a larger volume to be used in rapid SC injections with limited swelling, induration or pain.[5,6]

The open-label design used in this study will have no impact on the assessment of the PD, PK, and immunogenicity parameters and thus is not expected to impact the primary endpoint and most of the secondary endpoints. Importantly, a double blind study design would be more burdensome for the participants.

4.3. Justification for Dose

The selection of the efgartigimod IV dosage (10 mg/kg q7d) was made based on results from prior clinical studies, including a phase 3 study in participants with gMG (ARGX-113-1704). Administration of efgartigimod IV 10 mg/kg q7d for 4 infusions achieved near-maximal total IgG reduction, resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in participants with gMG. Furthermore, this dose was well tolerated with no safety concerns in all populations tested thus far.

The efgartigimod PH20 SC dose selected targets a similar total IgG reduction as compared to the efgartigimod IV 10 mg/kg dose, anticipating a similar clinical response. PK/PD modeling indicated that weekly or biweekly doses of efgartigimod PH20 SC 1000 mg result in a comparable effect on IgG levels when compared to efgartigimod IV 10 mg/kg administered q7d or biweekly (q2w).

No safety concerns have been identified to date with SC administration of efgartigimod PH20 SC in the completed phase 1 study ARGX-113-1901 or in ongoing studies in healthy subjects.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the ARGX-113-2001 study. A participant is considered to have completed the study if he/she completed the EoS visit at day 71 (±3 days), even if the participant did not complete treatment.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

1. Must be capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2. At least 18 years of age at the time of signing the ICF
3. Diagnosed with gMG with confirmed documentation and supported by at least 1 of the following:
    a. History of abnormal neuromuscular transmission demonstrated by single fiber electromyography or repetitive nerve stimulation
    b. History of positive edrophonium chloride test
    c. Demonstrated improvement in MG signs upon treatment with oral acetylcholinesterase (AChE) inhibitors as assessed by the treating physician
4. Meeting the clinical criteria as defined by the Myasthenia Gravis Foundation of America (MGFA) class II, III, IVa, or IVb
5. Abdominal skin tissue allows for absorption and assessment of local safety of the planned SC injection, as determined by the investigator
6. An MG-ADL total score of ≥5 points, with more than 50% of the score due to nonocular symptoms at screening and baseline
7. Receiving a stable dose of other gMG treatment (concomitant gMG treatment) prior to screening. For patients receiving nonsteroidal immunosuppressants (NSIDs), steroids, and/or AChE inhibitors as concomitant medications, the following dose conditions apply:
    a. NSIDs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months prior to screening and no changes to dose in the 3 months before screening
    b. Steroids: treatment initiated at least 3 months prior to screening and no dose changes in the month before screening
    c. AChE inhibitors: stable dose with no dose escalation during the 2 weeks before screening. AChE inhibitors must be withheld for at least 12 hours before the QMG assessment, to be consistent with the revised manual for the QMG test, as recommended by the MFGA
8. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies and:
    a. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last study dose of the IMP:
        – Refrain from donating sperm

Plus either

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

Or

- Must agree to use a male condom with a female partner using an additionally highly effective contraceptive method with a failure rate of <1% per year as described in Section 10.5. when having sexual intercourse with a woman of childbearing potential who is not currently pregnant

Or

- Be a sterilized man who has had a documented absence of sperm post-procedure

b. Female participants are eligible to participate if they are not pregnant or breastfeeding, and they are 1 of the following:

- Women of nonchildbearing potential (WONCBP), as defined in Section 10.5.1.

Or

- Women of childbearing potential (WOCBP) as defined in Section 10.5.1 and is using a contraceptive method that is highly effective (with a failure rate of <1% per year) during the study intervention and for at least 90 days after the last study dose of the IMP. The investigators should evaluate the potential for contraceptive method failure (eg, noncompliance) in relationship to the first dose of the study intervention
- WOCBP must have a negative highly sensitive serum pregnancy test within the screening period before the first dose of study IMP, see Section 8.2.8.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.8.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

5.2. Exclusion Criteria

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

1. Are pregnant or lactating, or intend to become pregnant during the study or within 90 days after the last dose of IMP
2. Has any of the following medical conditions:
   a. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection at screening
   b. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of myasthenia gravis or put the participant at undue risk

c. History of malignancy unless deemed cured by adequate treatment with no evidence of reoccurrence for ≥3 years before the first administration of the IMP. Participants with the following cancers can be included at any time:
   - adequately treated basal cell or squamous cell skin cancer
   - carcinoma in situ of the cervix
   - carcinoma in situ of the breast
   - incidental histological findings of prostate cancer (TNM Classification of Malignant Tumors stage T1a or T1b)

d. Clinical evidence of other significant serious diseases, or the participant has had a recent major surgery, or who have any other condition that, in the opinion of the investigator, could confound the results of the study or put the participant at undue risk

3. Worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, beta-blockers, etc.)
4. A documented lack of clinical response to plasma exchange (PLEX)
5. Received a live-attenuated vaccine fewer than 28 days before screening. Receiving an inactivated subunit, polysaccharide, or conjugate vaccine any time before screening is not exclusionary
6. Received a thymectomy <3 months prior to screening or 1 is planned to be performed during the study period
7. The following results from these diagnostic assessments will be considered exclusionary:
   a. Positive serum test at screening for an active viral infection with any of the following conditions:
      - Hepatitis B virus (HBV) that is indicative of an acute or chronic infection (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf, see Section 10.8)
      - Hepatitis C virus (HCV) based on HCV antibody assay
      - Human immunodeficiency virus (HIV) based on a CD4 count of ≤200 cells/mm^3 or test results that are associated with an acquired immunodeficiency syndrome (AIDS)-defining condition, such as: Cytomegalovirus retinitis with loss of vision, *Pneumocystis jiroveci* pneumonia, chronic intestinal cryptosporidiosis, HIV-related encephalopathy, *Mycobacterium tuberculosis* (pulmonary or extrapulmonary), or invasive cervical cancer
   b. Positive nasopharyngeal swab test for SARS-CoV-2
8. Using the following prior or concomitant therapies:
   a. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of IMP
   b. Use of any monoclonal antibody within 6 months before the first dose of the IMP

c. Use of Ig administered intravenously (IVIg), SC (SCIg), or intramuscularly within 4 weeks of screening
d. Use of PLEX within 4 weeks of screening
e. Previously participated in a clinical study with efgartigimod and/or products coformulated with rHuPH20 and received at least 1 administration of IMP

9. Total IgG levels <6 g/L at screening
10. Current or history of (ie, within 12 months of screening) alcohol, drug, or medication abuse
11. A known hypersensitivity reaction to efgartigimod, rHuPH20, or any of its excipients

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants will need to be fasted for each visit. Fasted is defined as no food or drink except for water for at least 8 hours prior to the visit. Water is allowed until 4 hours prior to the visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. Participants who fail to meet the eligibility criteria will be considered screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). See the eCRF completion guidelines for a complete list of what will be collected for screen failures.

Individuals who do not meet the criteria for participation in this study may be rescreened (ie, redoing the full assessments as per the Schedule of Activities (SoA) in Section 1.3. or retested once (ie, redoing assessments) after sponsor's written approval.

Examples of conditions under which rescreening may be considered include the following:

- Individuals who required treatment for an acute illness (eg, infection) may be rescreened once the illness is resolved or the medical problem stabilized.

Examples of conditions under which retesting may be considered include the following:

- Individuals who have clinical laboratory tests value meeting 1 or more exclusion criteria which are not in line with the medical history and clinical evaluation of the individual, may be retested to confirm the value of the tests, if still allowed within the screening period. If not feasible, the individual should be rescreened.

Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Delaying the administration of the IMP must occur if it is deemed in the best interest of the participant, as determined by the investigator. If the IMP cannot be administered within the specified time window, then that dose of the IMP must be missed. See Section 7.1.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention 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.

6.1. Study Intervention(s) Administered

Arm Name	Efgartigimod IV	Efgartigimod PH20 SC
Intervention name	Efgartigimod concentrate for solution for infusion [redacted] mg/mL, administered IV	Efgartigimod solution for SC injection [redacted] mg/mL coformulated with rHuPH20
Type	Biologic	Biologic
Dose formulation	Efgartigimod drug product of [redacted] mg/mL for dosing of 10 mg/kg for IV infusion	Efgartigimod drug product of [redacted] mg/mL for a fixed dose of 1000 mg for SC injection coformulated with 2000 U/mL rHuPH20
Unit dose strength(s)	[redacted] mg/mL	[redacted] mg/mL
Dosage level(s)	10 mg/kg q7d for a total of 4 infusions	1000 mg q7d for a total of 4 injections
Route of administration	IV infusion	SC injection
Use	Investigational	Investigational
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. The IMP will be labeled and packed in secondary containers in accordance with local laws and regulatory requirements.	The IMP will be provided in glass vials. Each glass vial will be labeled as per country requirement. The IMP will be labeled and packed in secondary containers in accordance with local laws and regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

For detailed instructions for the preparation, handling, storage, and accountability, please refer to the pharmacy manual.

6.2.1. Preparation

- Efgartigimod for IV administration will be provided as a sterile, colorless, clear concentrate for solution for infusion in glass vials. Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared at the site prior to administration.
- Efgartigimod for SC administration will be provided as a sterile, colorless to yellowish solution for injection in glass vials.
- The IMP will be manufactured in accordance with Good Manufacturing Practice regulations.

6.2.2. Handling

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive IMP and only authorized site staff may supply the IMP. IMP administration must be performed by site staff or, in the SC treatment arm only, by an adequately trained and supervised participant or caregiver. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

6.2.3. Storage

- The IMP will be supplied to the pharmacy at the designated investigational site by and under the responsibility of the sponsor's designated IMP supply vendor, who will also provide the investigator with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.
- The IMP must be stored refrigerated (2°C to 8°C or 35°F to 46°F) in its secondary packaging. It should not be exposed to freezing temperature or shaken, and it should be protected from direct sunlight during storage at the clinical site.
- The investigator (or his/her designee) is responsible for the correct and safe storage of the IMP assigned to the clinical site, in a locked, secure storage facility maintained within the appropriate temperature ranges, with access limited to those individuals authorized to dispense the IMP.

6.2.4. Accountability

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

- This is an open-label study; potential selection bias will be reduced by central randomization.

- Participants will be assigned a unique patient identification number at screening. Upon randomization, the participant will be assigned to a treatment arm according to the randomization schedule generated prior to the start of the study.
- Randomization will be stratified by Japanese versus non-Japanese participants. Within the non-Japanese participants, randomization will be further stratified by AChR-Ab status.

6.4. Study Intervention Compliance

- All participants will be dosed at the site. Participants in the SC treatment arm or their caregivers will be trained in self-administration of the IMP. These participants or their caregivers will receive specific training for self-administration or caregiver-supported administration and guidance on preparation, handling, storage and administration of the IMP. The first dose of efgartigimod PH20 SC must be administered by the investigator or designee, under medical supervision. After participants or caregivers are trained in administration, the subsequent doses of efgartigimod PH20 SC may be administered by the participant or caregiver under supervision by the investigator or designee (see Section 6.2.2). All administrations in the IV treatment arm will be performed by the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.
- The investigator should promote treatment compliance by stating that compliance is necessary for the participant's safety and the validity of the study. The prescribed dose, timing, and mode of administration cannot be changed. All dates, start and end times of IMP administration, and any deviations from the intended regimen must be recorded in the eCRF.
- A sponsor's designated contract research organization (CRO) monitor will review the pharmacy records at each site including the drug accountability and dispensing records on which the pharmacist or designated person should record all IMP released for participant use. The sponsor's designated CRO monitor will compare the dispensing record and vials with the individual participant's identifiers, kit number, and visit schedule to confirm that the participant received the correct treatment and dose, and that the dosing schedule is correct.

- Errors that are identified will be communicated to the site personnel to ensure that the errors are not repeated. The sponsor's designated CRO monitor's report will include details of any missed doses, errors in dose, treatment or scheduling errors, and the associated explanations. It will be evaluated if these dosing errors will be reported as protocol deviations in the clinical database. All supplies and pharmacy documentation must be made available throughout the study for the sponsor's designated CRO monitor to review.

6.4.1. Handling Missed Doses of the IMP

All efforts will be made to ensure that the participant receives all administrations of IMP on the scheduled day. If a participant misses any scheduled doses, he/she will not be discontinued from the study (see Section 7.1).

6.4.2. Protocol Deviations

The investigator should not implement any deviation from or changes to the approved protocol without agreement of the sponsor and prior review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority as per local regulation, except where necessary to eliminate an immediate hazard to study participants, or when the change involves only logistical or administrative aspects of the study (eg, change of telephone numbers). The investigator (or designee) should document and explain a deviation from the approved protocol.

6.5. Dose Modification

No dose modification is planned for this study.

6.6. Continued Access to Study Intervention After the End of the Study

At the EoS visit on day 71±3, participants will be offered the option to roll over into a single-arm, open-label, extension study (ARGX-113-2002) to receive efgartigimod PH20 SC 1000 mg. Participants who complete the study may be eligible to participate in the extension study.

6.7. Treatment of Overdose

For this study, any dose of efgartigimod IV or efgartigimod PH20 SC greater than 10% of the planned dosage amount (see Section 1.3) will be considered an overdose. There is no recommended specific treatment for an overdose of efgartigimod IV or efgartigimod PH20 SC. In case of suspected overdose, the participant should be treated according to standard medical practice based on the investigator's judgment. The suspected overdose should be documented in the source documents and the eCRF, including any observed AEs.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the start of the study or receives during the study must be recorded in the eCRF along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Brand name (for vaccines only)

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prior Medication and Procedures

Clinically relevant prior medication and procedures received by the participant must be recorded in the eCRF, including the start and stop dates of the therapy and if the therapy is ongoing.

Clinically relevant prior medications and procedures includes:

- Prior gMG medications and procedures from 1 year prior to screening, including the participant's response to the therapy and the reason for changing the medication or dose
- Prior non-gMG medication and procedures from 6 months prior to screening
- All available vaccination history. When a vaccine requires multiple doses (eg, influenza vaccine) or a booster, only the most recent vaccination must be recorded

6.8.2. Permitted Concomitant Medication and Procedures

Participants are required to be on a stable dose of concomitant therapy for gMG. (inclusion criterion 7). Permitted concomitant therapy for gMG includes:

- NSIDs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide)
- steroids
- AChE inhibitors

Administration of AChE inhibitors must be withheld for at least 12 hours prior to performing the QMG assessment. Complying with this requirement will not be considered a change in the patient's concomitant gMG treatment.

Participants are allowed to receive vaccines that do not use live or live-attenuated biological material. Any inactivated subunit, polysaccharide, or conjugate vaccine is allowed at the discretion of the investigator and when administered at least 48 hours predose or 48 hours postdose of the IMP. Any vaccination done within 28 days of screening until 28 days after the final dose of the IMP must be recorded in the eCRF with the brand name of the vaccine.

Standard therapies for concurrent medical conditions are permitted if they are not listed as prohibited in the following section.

6.8.3. Prohibited Medication and Procedures

Participants must discontinue from the study intervention if any prohibited therapies are used.

During the study, participants may NOT receive:

- any monoclonal antibody
- other experimental/study IMP
- live or live-attenuated vaccines
- a change in the dose or frequency of their current gMG medication
- a change in concomitant therapy for gMG
- PLEX, IVIg, immunoadsorption, or a change in dosage or type of corticosteroid used as a monotherapy or in combination

PLEX, Ig therapy (IVIg and SCIg), immunoadsorption, or a change in dosage or type of corticosteroid are considered rescue therapy if both of the following conditions apply:

1. The treating physician believes that the participant's health is in jeopardy if rescue therapy is not provided, and
2. The participant is deteriorating clinically according to the protocol-defined criteria, which includes at least 1 of the following:
   a. new or worsening of respiratory/bulbar symptoms, or
   b. at least a 2-point increase in any individual nonocular items on the MG-ADL scale as compared to the previous visit

The date and time of rescue medication administration, as well as the name, dosage regimen, and response to the rescue medication will be recorded in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Administration of the IMP may be withheld if, in the opinion of the investigator, it could put the participant at undue risk. If the IMP is being withheld and it cannot be administered during the scheduled time window, then that dose of IMP must be missed. The subsequent scheduled dose of IMP can be administered to the participant at the next scheduled treatment period (TP) visit if the investigator determines that the undue risk has been resolved. The participant may continue with the study even if they miss multiple doses.

It may be necessary for a participant to permanently discontinue study intervention.

Participants **must** discontinue the study intervention if:

- It is in the participant's best interest; discussion with the sponsor's medical director is encouraged prior to discontinuation
- The participant receives prohibited medication (Section 6.8.3)
- A severe hypersensitivity reaction to the IMP occurs
- The participant is pregnant
- The sponsor requests discontinuation (eg, following DSMB advice, see Section 10.1.5.1)

If study intervention is permanently discontinued, the participant will remain in the study and will complete all scheduled visits and the EoS visit on day 71 (±3 days), even though the participant will not receive any more doses of the IMP. See the SoA (Section 1.3) for data to be collected at the EoS visit.

7.2. Participant Discontinuation/Withdrawal From the Study

- Early discontinuation from the study is defined as the permanent cessation of further participation in the study prior to its planned completion.
- The reason for early discontinuation from the study will be clearly documented by the investigator.
- A participant may withdraw from the study at any time at his/her own request.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- Participants who discontinue from the study will not be replaced. The sample size is inflated to account for attrition. See Section 9.2.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this request in the site study records and inform the sponsor as soon as possible.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be addressed by the site staff upon occurrence or awareness. The investigator may decide whether to discontinue the IMP. If possible, the sponsor should be involved in the decision.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed, and confirmed by the sponsor and/or the sponsor's designated CRO to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- At screening, all eligibility assessments should be performed after obtaining informed consent.
- When a protocol-required procedure cannot be performed, the investigator will document the reason, and any corrective and preventative actions that he/she has taken to ensure that the protocol processes are adhered to in the source documents. The study team should be informed of these incidents in a timely manner. These incidents will be considered a protocol deviation and will be recorded accordingly.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. Pharmacodynamics

Total immunoglobulin G (IgG), IgG subtypes (IgG1, IgG2, IgG3, and IgG4) levels, and AChR-Ab levels will be measured using validated methods from blood sampled as indicated in Section 1.3. AChR-Ab levels will only be measured in AChR-Ab seropositive participants. The actual date and time of the blood sample collection will be collected and included in the central laboratory data transfer.

8.1.2. Clinical Efficacy Assessments

The MG-ADL and the QMG assessments should be administered by the same evaluator throughout the study for a given participant when possible. It is recommended to perform the MG-ADL scale prior to all other assessments.

8.1.2.1. MG-ADL

The MG-ADL is an 8-item patient-reported scale that assesses MG symptoms and their effects on daily activities. It evaluates a participant's capacity to perform different activities in their daily life, including talking, chewing, swallowing, breathing, brushing their teeth, combing their hair, or getting up from a chair. The MG-ADL also assesses double vision and eyelid droop. It is a discrete quantitative variable in which the 8 items are rated by the participant on a scale of 0 to

3. The total score can range from 0 to 24, with higher total scores indicating more impairment. The MG-ADL assessment does not require any equipment to perform. The scoring of the MG-ADL should be performed by a trained and certified evaluator.

8.1.2.2. QMG

The QMG quantifies disease severity based on impairments of body function and structures as defined by the International Classification of Functioning, Disability and Health. The QMG consists of 13 items that assess ocular, bulbar, and limb function. Six of the 13 items are timed endurance tests measured in seconds. Each item has a possible score from 0 to 3. The total possible score is 39, where higher total scores indicate more severe impairments. It is based on qualitative testing of specific muscle groups to assess limb function. The QMG requires minimal equipment, such as a spirometer, mouthpieces that fit the spirometer, nose clips, a stopwatch, cups and water for the swallowing tests, a goniometer, and a dynamometer. The scoring of the QMG should be performed by a trained evaluator and the scoring is based on the evaluator's examination.

8.1.3. Myasthenia Gravis Quality of Life Questionnaire (15-item Scale Revised)

The Myasthenia Gravis Quality of Life Questionnaire (15 item scale revised) (MG-QoL15r) is a 15-item survey of a patient's perceived health-related quality of life and addresses attributes known to be meaningful to a patient with gMG, such as psychological well-being and social functioning. The patient assesses statements using a 3-point (0–2) Likert scale on the following domains:

- mobility (9 items)
- symptoms (3 items)
- general contentment (1 item)
- emotional well-being (2 items)

Each item will be participant-scored using a 3-point severity scale ranging from 0 (not at all) to 2 (very much), with a maximum possible score of 30. The MG-QoL15r is helpful in determining the participant's perception of the extent and dissatisfaction of MG-related dysfunction.

8.1.4. EuroQoL 5 Dimensions 5 Levels

The EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) is a standardized measure of health status and 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

Each dimension has 5 levels:

- no problem
- slight problem
- moderate problem
- severe problem
- extreme problem

The participant will be asked to indicate his/her health state by ticking (or placing an "x" in) the box against the most appropriate statement in each of the 5 dimensions. 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, while state 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.

A visual analog scale 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."

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Demographics

Demographic characteristics comprise age, year of birth, gender, race, and ethnicity (per local regulations). Source data verification will be performed on race and ethnicity unless it is prohibited by local regulations.

8.2.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the participant's general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological systems.
- Height will be measured at screening only.
- Weight will also be measured at screening, baseline, and at the EoS visit. The participant is allowed to wear indoor daytime clothing with no shoes.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3. Vital Signs

- Vital signs (to be taken before blood collection for laboratory tests) will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.
- It is recommended that the method used to measure body temperature at screening is maintained throughout the study.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.4. Electrocardiograms

Single 12-lead ECG will be obtained after the participant has rested in a supine position for 5 minutes as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures time between heart beats (RR), atrioventricular nodal delay (PR), duration of ventricular depolarization (QRS), total duration of ventricular depolarization (QT), and rate-corrected QT intervals using Fridericia's formula (QTcF). ECGs will be performed predose on dosing days.

8.2.5. Medical and Surgical History

Medical history will include:

- All relevant medical history (eg, significant findings, surgeries and pre-existing conditions present at screening) must be recorded in the eCRF regardless of whether it is related to gMG.
- Previous emergency room (ER) visits, hospitalizations, and intensive care unit (ICU) admissions from 1 year prior to screening, including the number of days admitted.
- Abnormalities in physical examination, vital signs and ECG at screening must be reported as medical history in eCRF. At all other visits, new abnormal or worsened pre-existing conditions will be reported as AE.

8.2.6. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual. The actual sample collection date and time must be collected in the participant's source document and included in the central laboratory data transfer.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

- All routine laboratory safety assessments must be performed by the central laboratory.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If any values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from nonprotocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the outcomes must be recorded.

8.2.6.1. Hematology, Clinical Chemistry, and Urinalysis

Blood and urine samples for clinical safety laboratory assessments, including hematology, blood chemistry, and urinalysis, will be collected at the timepoints specified in the SoA (Section 1.3). The list of clinical safety laboratory parameters for hematology, clinical chemistry, and urinalysis are provided in Table 3.

- Blood samples for clinical laboratory assessments will be taken while the participant is in the fasted condition, defined as no food or drink (except for water) for 8 hours. Water is permitted up to 4 hours prior to the assessment.
- Blood samples for safety assessments will be collected according to the laboratory manual.
- The samples will be analyzed at the central laboratory.
- Clinical laboratory tests will be reviewed for potential clinically significant findings at all time points throughout the study. Findings meeting the definition of an AE (see Section 10.4) must be recorded on an AE page of the eCRF. See Section 10.4.3 for information on following up of clinically significant abnormalities.
- Laboratory tests with values considered clinically significantly abnormal during the study that meet the definition of an AE will be monitored until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

8.2.6.2. Virus Serology

For exclusion criterion 7.a, blood will be sampled and evaluated for virus serology as described in Section 10.2.

8.2.6.3. Follicle-Stimulating Hormone Level

Female participants must have their follicle-stimulating hormone (FSH) level measured at the time points listed in the SoA (Section 1.3) as described in Section 10.2.

8.2.6.4. SARS-CoV-2 Test

Nasal and throat mucosal cell samples will be collected according to the laboratory manual at the time points specified in the SoA (Section 1.3) to be tested for SARS-CoV-2.

8.2.7. Assessment of Administration Site

The injection site of participants receiving efgartigimod PH20 SC will be continuously assessed by the participant (see Section 1.3). On dosing days, the assessment will be performed by the investigator prior to dosing and 1 hour after dosing. After participants have received efgartigimod the assessment will include asking the participants about any injection site reactions that occurred between visits. Any injection site reaction will be reported as an AE (Section 8.3).

8.2.8. Pregnancy Testing

- Refer to inclusion criteria 8.b for pregnancy testing entry criteria.
- Pregnancy testing at screening will be a highly sensitive serum test, and all subsequent pregnancy testing will be done using urine tests. Pregnancy testing should be conducted as indicated in the SoA (Section 1.3) during the study. If local regulations require more frequent or sensitive testing, then the local regulations will be followed.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.2.9. Immunogenicity

8.2.9.1. ADA Against Efgartigimod

Blood samples will be collected to assess the serum levels of ADA against efgartigimod as indicated in the SoA (Section 1.3). Sampling will be done predose on IMP administration visits.

As per regulations, all samples will be analyzed in a 3-tiered approach using validated methods[8]:

1. First, all samples will be evaluated in a screening assay (tier 1) and scored as ADA positive or negative.

2. Samples that screen positive in tier 1 will be evaluated in the confirmatory ADA assay to assess the specificity of the ADA response. The samples will be scored as either confirmed positive (ie, positive immunodepletion) or confirmed negative (ie, negative immunodepletion).
3. Samples confirmed to be positive for ADA in tier 2 will be further analyzed in a titration assay to characterize the magnitude of the ADA response and a neutralizing antibody (NAb) assay to assess the ADA for neutralizing activity.

If no sample was taken, the reason will be recorded.

8.2.9.2. ADA Against rHuPH20

Blood samples will be collected to assess the plasma levels of ADA against rHuPH20 as indicated in the SoA (Section 1.3). Sampling will be done predose on IMP administration visits.

As per regulations, all samples will be analyzed in a 3-tiered approach using validated methods[8]:

1. First, all samples will be analyzed in a screening assay (tier 1), which identifies putative positive or negative samples.
2. Samples that screen positive in tier 1 will be evaluated in the confirmatory ADA assay to assess the specificity of the ADA response. The samples will be scored as either confirmed positive or negative.
3. Samples confirmed to be positive for ADA in tier 2 will be further analyzed in a titration assay to characterize the magnitude of the ADA response and a neutralizing antibody (NAb) assay to assess the ADA for neutralizing activity.

If no sample was taken, the reason will be recorded in the relevant section of the eCRF.

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

- Efgartigimod is being developed for a neurologic indication, so suicidal ideation and risk behavior monitoring (SIB) is required.
- Participants being treated with efgartigimod should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases.
- Participants who experience signs of suicidal ideation or behavior, should undergo a risk assessment. All factors contributing to suicidal ideation and behavior (SIB) should be evaluated and consideration should be given to discontinuation of the study intervention.
- Baseline assessment of suicidal ideation and behavior and intervention emergent suicidal ideation and behavior will be monitored by asking the following question derived from the Patient Health Questionnaire (PHQ) item 9: "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?"

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

- The definitions of AEs and SAEs can be found in Section 10.4.
- AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).
- The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).
- An unexpected AE is any adverse drug event, which is not listed in the reference safety information in the current IB or is not listed at the specificity or intensity that has been observed in the current study.
- Suspected adverse drug reaction means any AE for which there is a reasonable possibility that the IMP caused the AE.
- Each AE is to be evaluated for duration, severity (using the Common Terminology Criteria for Adverse Events [CTCAE] criteria version 5.0), seriousness, and causal relationship to the IMP or study procedures. The action taken with the investigational drug and the outcome of the event must also be recorded.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected from the signing of the ICF until the EoS visit at the time points specified in the SoA (Section 1.3).
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from awareness of the site staff, as indicated in Section 10.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (AESI) as defined in Section 8.3.6 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- The sponsor (or its designee) will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authorities and the IEC/IRB as per applicable regulatory requirements. The sponsor (or its designee) will also be responsible to forward SUSAR reports to all investigators involved in the study, who will also be required to report these SUSARs to their respective IECs/IRBs, as per their local regulatory requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 90 days after the last dose of the study IMP.
- Attempts will be made to obtain details of all pregnancies in female partners of male participants that occurred after the start of study intervention and until 90 days after the last dose of IMP. Female partners will be asked to sign a relevant ICF.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- If a female partner of a male participant consents, the female partner will be followed to determine the outcome of the pregnancy. In this case, the investigator will collect follow-up information on the female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants or pregnant female partners of former male study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention and will continue with all remaining visits, including the EoS visit.

8.3.6. Adverse Events of Special Interest

An AESI is an event of scientific and medical concern specific to the sponsor's product or program (eg, an underlying condition being investigated, a mechanism of action/potential immunosuppression). An AESI can be serious or nonserious and related or unrelated to study IMP or procedures. Further characterizing information will be collected in the eCRF.

Efgartigimod treatment induces reductions in the IgG levels and there is a potential risk for infections associated with low IgG levels. As such, any infections are considered AESIs in this study. Further information to be collected in the eCRF will include:

- Location of the infection
- Relationship to the underlying condition, medical history, and concomitant medications
- Reoccurrence of previous infection
- Previous rescue therapy
- Any confirmatory procedure, culture, or urgent medical intervention

8.4. Pharmacokinetics

- Blood samples for pharmacokinetics (PK) will be collected from each participant as specified in the SoA (Section 1.3). Concentrations of efgartigimod will be determined using a validated method.

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples collected for analyses of efgartigimod concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- At visits during which blood samples for the determination of multiple aspects of efgartigimod will be taken, 1 sample of sufficient volume can be used.
- For the efgartigimod IV treatment arm, PK sampling will be performed both predose (within 1 hour prior to the start of the infusion) and postdose (within 1 hour after the end of the infusion) on dosing days. For the efgartigimod PH20 SC treatment arm, PK sampling will only be done predose (within 1 hour prior to the injection) on dosing days.
- The following PK parameters will be measured: C_{max} of efgartigimod (after all doses for the IV treatment arm) and C_{trough} of efgartigimod in both arms.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

See Section 8.1.1 for assessments of total IgG levels, IgG subtype levels, and AChR-Ab levels.

8.7. Immunogenicity Assessments

See Section 8.2.9 for immunogenicity assessments.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data including ER visits, hospitalizations, and ICU admissions for any reason from 12 months prior to screening will be collected as medical history. All hospitalizations, ER visits, and ICU admissions will be collected during the study and analyzed, even if they are not classified as AEs, to compare medical resource utilization before and after efgartigimod treatment. These data will also be collected in the extension study ARGX-113-2002.

8.9. Storage of Blood Samples After the Study

Any samples remaining after the laboratory analyses defined in the protocol have been completed may be stored for up to 15 years after the end of the study for additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or gMG. The samples may be stored in the laboratory or long-term storage designated by the sponsor or research partners worldwide. The storage and future use of samples obtained during this study is permitted unless local regulations do not allow it or if the participant did not consent.

In addition, blood samples may be used to validate methods to measure efgartigimod, antibodies, and biomarkers.

9. STATISTICAL CONSIDERATIONS

The statistical analysis will be performed by the sponsor's designated CRO using statistical analysis systems (SAS) software (SAS Institute, Cary, NC, United States) version 9.4 or higher, and the software package R, if applicable. The standard operating procedures (SOPs) and work instructions of the sponsor's designated CRO will be used as the default methodology if not otherwise specified.

A detailed and comprehensive Statistical Analysis Plan (SAP) will be written and signed-off prior to final analysis database lock. Minor changes to the statistical methods set out in this protocol do not require a protocol amendment but will be documented (as changes from the protocol) in the SAP and in the clinical study report(s). The below sections contain the main general features of the statistical analysis. More details will be provided in the SAP.

9.1. Statistical Hypotheses

The confirmation of the noninferiority (NI) of efgartigimod PH20 SC with efgartigimod IV will be based on the total IgG percent reduction at day 29 utilizing a noninferiority margin of 10. See Section 9.2 for justification of the noninferiority margin. The hypotheses for the evaluation of noninferiority are as follows:

- Null hypothesis: the difference in percent reduction from baseline of total IgG at day 29 for the SC treatment arm as compared to the IV treatment arm will be ≥10 (ie, $\mu_{IV} - \mu_{SC} \geq 10$)
- Alternate hypothesis: the difference in percent reduction from baseline of total IgG at day 29 for the SC treatment arm as compared to the IV treatment arm will be <10 (ie, $\mu_{IV} - \mu_{SC} < 10$)

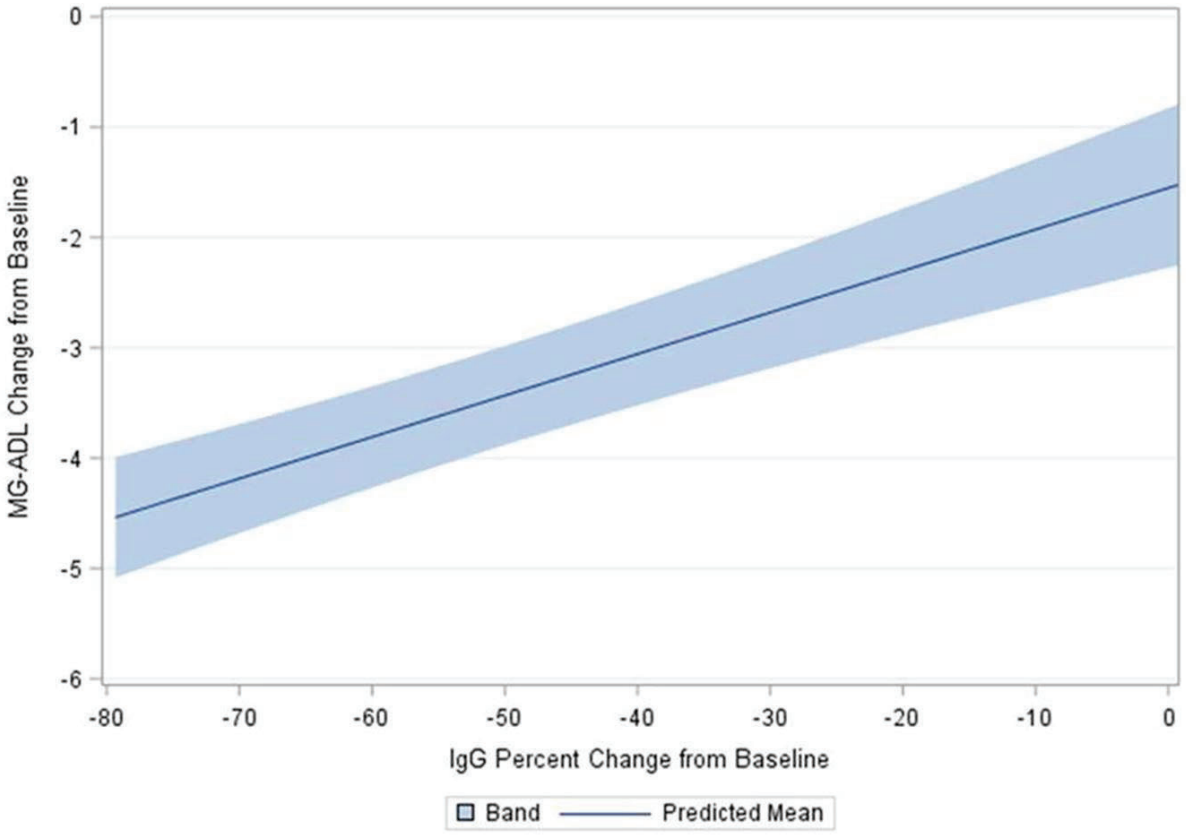
9.2. Sample Size Determination

The noninferiority (NI) evaluation will be based on the percent reduction from baseline in total IgG levels at day 29.

To evaluate the relationship between changes in total IgG and MG-ADL, statistical modeling on MG-ADL change from study baseline with total IgG percent reduction from study baseline as a predictor and participant as a random effect was performed among all study ARGX-113-1704 participants on the efgartigimod IV 10 mg/kg treatment arm in the modified intention-to-treat (mITT) analysis set. Data from all cycles in the study were included. To minimize potential modeling bias introduced by outlier data points, only week 1 to week 6 data were included and data after week 6 were excluded. The modeling results demonstrate that total IgG percent change from study baseline and MG-ADL change from study baseline were highly correlated (p-value <0.0001) as illustrated in Figure 2. With a difference of 10 in the mean total IgG percent reduction (eg, from total IgG percent reduction of 63 to total IgG percent reduction of 53) the mean difference in MG-ADL improvement (ie, decrease from baseline) is expected to be 0.35 (2-sided 95% confidence interval, 0.236 to 0.465). In the phase 3 study ARGX-113-1704, the mean of MG-ADL improvement at week 4 of cycle 1 was 4.5 (standard error 0.36) in the efgartigimod treatment group and 2.0 (standard error 0.27) in the placebo treatment arm, which translates to a treatment effect of 2.5 (2-sided 95% confidence interval, 1.62 to 3.38). The corresponding mean of total IgG percent reduction at week 4 of cycle 1 was 62.2 (standard error

0.82) in the efgartigimod treatment arm and 0.1 (standard error 2.23) in the placebo treatment arm, which translates to a treatment effect of 62.1 (2-sided 95% confidence interval, 57.44 to 66.76). With a NI margin of 10 in IgG percent reduction, 84% (1–10/62.2 x 100%) of the PD effect as assessed by total IgG reduction is expected to be preserved, whereas 86% (1–0.35/2.5 x 100%) of the clinical effect as assessed by MG-ADL change is expected to be preserved.

Figure 2: Statistical Modeling on MG-ADL Change From Baseline With IgG Percent Reduction From Baseline as a Predictor and Patient as a Random Effect in All Efgartigimod IV Treated Patients in Study ARGX-113-1704 (mITT Analysis Set)



IgG= immunoglobulin G; IV=intravenous(ly); MG-ADL=Myasthenia Gravis Activities of Daily Living; mITT=modified intention-to-treat
Note: To minimize potential modeling bias introduced by outlier data points, only week 1 to week 6 data from all cycles in study ARGX-113-1704 were included.

Based on data from the phase 3 study ARGX-113-1704, the mean percent decrease in total IgG levels with the IV formulation is expected to be approximately 62 (standard deviation 7.5). Assuming the total IgG percent reduction from baseline with the SC formulation is 60 (2 less compared to the IV formulation) along with a standard deviation of 7.5, 20 participants per treatment arm are needed to reach 90% power to detect noninferiority using a 1-sided 2-sample t-test at a 2.5% level of significance. To account for participant discontinuation, 3 additional participants per treatment arm have been added. A sample size of 46 participants will need to be enrolled and randomized, allowing for a 13% attrition rate.

The assumptions utilized in the sample size calculations will be evaluated in study ARGX-113-1907**,** which will compare the PD, PK, safety, and tolerability of multiple doses of efgartigimod PH20 SC and efgartigimod IV in healthy participants. Study ARGX-113-1907 will use the same dosage as in the current study and will provide a detailed assessment of the PD effect in healthy participants, which is expected to represent the effect in participants with gMG. If the results of study ARGX-113-1907 indicate that the pooled standard deviation of the mean percent decrease in total IgG levels is larger than 7.5, the sample size will be adapted accordingly. If the pooled standard deviation is:

- 8.5, then a total of 50 participants will be recruited, with 6 additional participants added to account for discontinuations for a total of 56 participants (based on a pooled standard deviation of 8.5)
- 10.0, then a total of 68 participants will be recruited, with 8 additional participants added to account for discontinuations for a total of 76 participants (based on a pooled standard deviation of 10)

Seventy-six participants would suffice for the noninferiority comparison between SC and IV based on IgG reduction at day 29; however, increasing the sample size to approximately 110 participants will provide better quantification of the clinical safety and efficacy profile of the SC formulation in patients with gMG while the IV formulation will serve as a reference treatment in this randomized study.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened to determine eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol. "Randomized" means that an enrolled participant has been randomly assigned to a treatment arm.

9.3. Analysis Sets

The following analysis sets are defined:

Table 2: Analysis Sets

Analysis Sets	Description
Safety analysis set	All randomized participants who are exposed to the IMP
Intention-to-treat set	All randomized participants with a value for total IgG levels at baseline and at least 1 post-baseline timepoint
PK analysis set	Subset of safety analysis set with at least 1 postdose PK measurement

9.4. Statistical Analyses

The SAP will be finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the

planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

- The baseline value will be defined as the last assessment prior to the first administration of efgartigimod.
- All study visits will be recalculated based on actual dates and will be referred to as "analysis visits," which will be used in the statistical analyses. The rules for calculating the analysis visits will be documented in the SAP. Rules for inputting partial dates or missing dates will also be documented in the SAP.

9.4.2. Primary Endpoint

Definition of the Estimand for the Primary Endpoint

- Population: intention-to-treat (ITT) analysis set (see Table 2)
- Variable: Percent reduction from baseline in total IgG levels at day 29
- Main intercurrent events:
  - early treatment discontinuation for any reason prior to day 29
  - initiation of Ig therapy (IVIg and SCIg) as rescue therapy prior to day 29
  - missed doses

Handling of Main Intercurrent Events

For early treatment discontinuation or missed doses, the observation captured 7 days after the last dose will be used. If Ig therapy is used as rescue therapy prior to day 29, the last observation prior to the initiation of Ig therapy will be used.

Estimation of Treatment Effect and Statistical Inference

An analysis of covariance model (ANCOVA) will be used to estimate the mean percent reduction in total IgG levels from baseline at day 29 for each treatment arm, as well as the 2-sided 95% confidence interval for the difference between the 2 treatment arms. The model will include treatment as a factor and baseline total IgG level as a covariate.

When the upper limit of the 95% confidence interval (mean percent reduction with IV – mean percent reduction with SC) is below the margin of 10, the SC formulation will be considered noninferior to the IV formulation.

Complementary Analyses

To facilitate interpretation of the estimated treatment effect in the primary analysis, sensitivity analyses will be conducted where the main intercurrent events will be handled differently. Details will be provided in the SAP.

9.4.3. Secondary Endpoints

All secondary endpoints will be summarized with descriptive statistics by treatment arm and overall among all participants in an appropriate analysis set. Categorical variables will be summarized with the number and percent of participants in each category. Continuously variables will be summarized with N, mean, standard deviation, 95% 2-sided confidence interval, median, first quartile (Q1), third quartile (Q3), minimum, and maximum.

In addition, the difference in the percentage of MG-ADL responders between the 2 treatment arms will be analyzed using the meta-analysis predictive approach while incorporating the treatment cycle 1 data from the efgartigimod IV treatment arm in study ARGX-113-1704 as historical active controls.[7]

9.4.4. Exploratory Endpoints

Exploratory endpoints will be summarized with descriptive statistics by treatment arm and overall among all participants in the ITT analysis set.

9.5. Interim Analysis

Interim analyses may be performed to support questions from authorities and/or submissions.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2. Financial Disclosure

The sponsor will fund the study as outlined in the clinical study agreement.

The sponsor will obtain adequate global/local insurance for the study participants including the study participants for the required duration of time.

The sponsor maintains an insurance coverage for this study in accordance with the laws and regulations of the countries in which the study is performed. Liability and insurance provisions for this study are specified in the investigator's contract. The terms and conditions will apply as specified in the policy document.

Investigators and sub-investigators will provide the sponsor with sufficient accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigator are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Prior to signing the ICF, the study participants will be instructed not to participate in any other clinical study that involves a therapeutic intervention until the completion of the study.
- Any participant that provides informed consent will be assigned a unique participant ID via the Interactive Response Technology (IRT) system.
- The investigator or his/her representative will explain to the participant all of the following: the nature of the study, its purpose, the procedures involved, the expected duration, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available, and the extent of maintain the confidentiality of the participant's records. The investigator or his/her representative will answer all questions from the participant regarding the study.
- Participants must be informed that their participation is voluntary, that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.
- Participants will be required to sign a statement of informed consent, after receipt of detailed information on the study, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The ICF will be used to explain the potential risks and benefits of study participation to the participant in simple terms before the participant is screened.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A separate ICF will be issued in case of pregnancy of a female partner of a male participant. If required by local regulations, a separate pregnancy ICF will be issued for female participants who become pregnant.
- All participant information and ICFs must be available in the local and vernacular languages required at the site and include participant information sheets/brochures

that outline the study procedures. All ICF(s) must be signed and dated by the participant.

- Participants must reconsent to the most current version of the ICF(s) during their participation in the study.
- The investigator is responsible for ensuring that informed consent is obtained from each participant and for obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of the IMP.
- A copy of the signed and dated ICF(s) must be provided to the participant.
- A participant who is rescreened or retested is not required to sign another ICF if the rescreening occurs within the screening period.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Safety Monitoring Board

- Participant safety will be monitored by an independent DSMB, which includes safety signal detection at any time during the study.
- The DSMB will consist of an independent group of clinical experts who are not involved in the study management. The objective of the DSMB will be to review and evaluate all available safety data. The planning and frequency of the meetings will be detailed in the DSMB charter. Additionally, ad hoc meetings can be requested at any time during the study by the sponsor or the DSMB.
- The DSMB will advise the sponsor regarding continuation, modification, temporary discontinuation, or termination of the study after every meeting.
- The composition, objectives, role, and responsibilities of the DSMB will be described in the DSMB charter, which will be agreed to by the DSMB members and the

sponsor. The DSMB charter will also define and document the content of safety summaries and general procedures, including communications.

10.1.6. Dissemination of Clinical Study Data

- The sponsor or designee and auditor may access participant records for the purpose of monitoring this study, auditing, and managing progress details. The investigator must be fully aware that the sponsor or designee and auditor can inspect or verify documents to verify participant's chart and eCRF records. Such information must be kept confidential in locked facilities that allow for this. The investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each participant screened for the study.
- The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor's designated CRO monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of duration of participation or administration of IMP (ie, an eCRF has to be submitted for screen failures as well). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and participant number. Any personal information, including participant name, should be removed or rendered illegible to preserve data privacy.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF if and where applicable. No source data verification will be performed on race and ethnicity only if requested per local regulations.
- Guidance on completion of eCRFs will be provided in the eCRF completion guidelines by the designated CRO.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7.1. Data Handling and Record Keeping

It is the investigator's responsibility to maintain essential study documents (records and documents pertaining to the conduct of this study and the distribution of IMP, including regulatory documents, eCRFs, signed participant ICFs, laboratory test results, IMP inventory records, source documents, relevant correspondence, AE reports, and all other supporting documentation) as required by the applicable national regulatory requirements. The study site should plan on retaining such documents for approximately 25 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the IMP. The sponsor will notify the principal investigator of these events.

These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Participant identification codes (participant names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the sponsor, who agrees to abide by the retention policies. The investigator is required to notify the sponsor (or an authorized representative) in writing prior to changing the location or status of any essential clinical study documents. The investigator must contact the sponsor prior to disposing of any study records.

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

For studies conducted outside the US under an US investigational new drug (IND), the principal investigator must comply with US Food and Drug Administration IND regulations and with those of the relevant national and local health authorities.

10.1.7.2. Quality Assurance Audit

Study processes, study sites (including, but not limited to site visits, central laboratories, vendors), the study database, and study documentation may be subject to quality assurance audit during the course of the study by the sponsor or sponsor's designee (CRO or other vendor) on behalf of sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion. Such audits/inspections can occur at any time during or after completion of the study.

10.1.7.3. Quality Control

Quality control will be applied to each stage of study-related activities.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meetings
- Central laboratories for clinical laboratory parameters
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Ongoing oversight by sponsor's designated CRO monitors of safety parameters and adherence to selection criteria
- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the clinical study report (CTR)
- To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations

In addition, periodic audits can be performed as specified in Section 10.1.7.2.

When audits or inspections are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the data management plan.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- All information regarding ARGX-113 supplied by the sponsor to the investigator and all data generated as a result of this study are considered confidential and remain the sole property of the sponsor. The results of the study will be reported in a clinical study report (CSR). The CSR will be written in accordance with the ICH E3 guideline and will be submitted in accordance with local regulations.
- Any manuscript, abstract, other publication, presentation of the results, or information arising in connection with the study must be prepared with the sponsor and must be submitted to the sponsor for review and comment prior to submission for publication

or presentation. Study participant identifiers will not be used in the publication of results.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 3: Protocol-Required Laboratory Tests

Laboratory Assessment	Parameters		
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) %Reticulocytes	White blood cell count with differential (% and absolute numbers) Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen (BUN) Creatinine Glucose (fasting for 8 hours) Calcium Glycosylated hemoglobin (HbA1c) Potassium Sodium Alkaline phosphatase (ALP)[a] Lactate dehydrogenase (LDH)	C-reactive protein (CRP) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) γ Glutamyl transferase (GGT) Bilirubin, total and direct Albumin	Cholesterol: Total LDL HDL Triglycerides International Normalized Ratio (INR) Activated Partial Thromboplastin Time (aPTT)
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (for female participants of childbearing potential) Microscopic evaluation		
Screening tests	Virology: HIV 1&2 screen/p24 antigen, hepatitis B core, hepatitis B surface, and hepatitis be surface antigen; and hepatitis C antibody, SARS-CoV-2 testing Highly sensitive serum hCG pregnancy test (for female participants of childbearing potential) Total immunoglobulin (IgG) levels AChR-Ab serology Follicle-stimulating hormone (FSH) (for female participants)		

[a] If alkaline phosphatase is elevated, consider fractioning.

10.3. Appendix 3: Total Blood Volume Collected From Each Participant

The maximum amount of blood collected from each participant is 350 mL. Repeat or unscheduled samples may be taken for safety reasons or technical issues with samples.

10.4. Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events to Be Collected as AEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT to Be Collected as AEs

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

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

10.4.3. Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE form.

- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator will make an assessment of intensity for each AE and SAE reported during the study.

All AEs observed will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The grade refers to the severity of the AE. If a particular AE's severity is not specifically graded by the guidance document, the investigator is to use the general NCI CTCAE definitions of grade 1 through grade 5 following his/her best medical judgment, using the following general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone)
- Grade 3: Severe; or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4: Life-threatening consequences or urgent intervention indicated
- Grade 5: Death related to an AE

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE as "related" or "not related."
- The investigator will use clinical judgment to determine whether there is a reasonable possibility that the IMP caused the AE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP

administration is compelling and/or follows a known or suspected response pattern concerning that IMP.

- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP and the AE.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.4.4. Reporting of SAEs

SAE Reporting via Paper Data Collection Tool

- All SAEs will be recorded on the paper SAE report form and the AE form in the eCRF. The investigator or designated study staff should check that all data entered are consistent.
- When the SAE is entered in the eCRF, an alert email for the SAE report in the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the electronic data capture system.
- The paper SAE report form should be faxed or emailed to the sponsor's designated CRO.
- Contacts for SAE reporting can be found in Safety Mailbox/Fax on page 2.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Women of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to 1 of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

d. For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

1. Postmenopausal female
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
      – A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
      – Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] oral intravaginal transdermal injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] oral injectable
Sexual abstinence

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together due to risk of failure from friction

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

10.6. Appendix 6: Administrative Structure

Table 4: List of Vendor Information

Country	Address of Vendor
Clinical laboratories for safety sample analysis	
United Kingdom	[redacted]
Analysis of PK, PD, and ADA	
United Kingdom	[redacted]
United States	[redacted]
France	[redacted]
Study monitoring/medical monitoring	
United Kingdom	[redacted]
Clinical study supply management	
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
Data management and biostatistics	
Belgium	[redacted]
Drug safety reporting	
United States	[redacted]

10.7. Appendix 7: Possible Adaptations to Study Protocol During the COVID-19 Pandemic

During the coronavirus disease-2019 (COVID-19) pandemic, study sites and participants are facing unprecedented challenges. As a result of this crisis, the sponsor has considered changes that are necessary to protect the safety of the participants as well as the site staff, while still evaluating the noninferiority of efgartigimod PH20 SC as compared to efgartigimod IV. All sites and participants will follow local regulations and guidance regarding preventing the spread of COVID-19.

The risk assessment, risk mitigation plan, and changes that may occur in response to an increase in COVID-19 cases is described in the following sections.

10.7.1. COVID-19 Risk Assessment for Participant Safety

Efgartigimod administration results in the reduction of all immunoglobulin G (IgG) subtypes, potentially hindering immune response and increasing the risk of all infections, including COVID-19. However, efgartigimod does not affect the levels of other immunoglobulin subtypes, such as IgA and IgM. Also, previous studies have shown that the maximum mean reduction of total IgG ranges from 60% to 70% and total IgG levels return to baseline within a few weeks of stopping efgartigimod treatment. Furthermore, other elements of the immune system are not impacted by efgartigimod treatment. The doses used in study ARGX-113-2001 have been administered to over 250 participants, including healthy volunteers and patients with generalized myasthenia gravis (gMG), immune thrombocytopenia (ITP), and pemphigus, with no infection-related safety concerns identified. Therefore, despite the immunomodulating properties of efgartigimod, efgartigimod treatment is not expected to increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or developing COVID-19 in participants.

10.7.2. COVID-19 Risk Mitigation

All participants with clinically significant uncontrolled infections, malignancies, recent surgeries, and/or the presence of certain viral infections are excluded (see Section 5.2). The screening tests include a test for SARS-CoV-2 and a positive test excludes the participant. If at any point a participant tests positive for SARS-CoV-2 or reports COVID-19 symptoms, they will be discontinued from the study intervention. Furthermore, administration of efgartigimod to a participant will be interrupted if a clinically significant infection occurs. Infections are also considered an AESI subject to structured safety reporting and a detailed questionnaire, so a participant contracting COVID-19 would be recorded as an AESI.

During the entire study the sites will implement all recommendations issued by the local government regarding minimizing the spread of COVID-19 (eg, social distancing, disinfection, hygiene, face mask requirements, and use of personal protection equipment [PPE] by site staff), including specific guidelines related to clinical research performed in clinical research centers.

10.7.3. Possible Changes in Study Design Due to the COVID-19 Pandemic

10.7.3.1. Implementation of This Appendix

Implementation for all sites includes social distancing where possible, PPE, and a telephone call before each study visit to check for COVID-19 symptoms. The adaptations to the visits and procedures described are acceptable alternatives to the main protocol procedures only under exceptional circumstances and after approval of the sponsor and/or CRO. Approval will be granted based on the possibility of participants going to the site and per local and/or site regulations.

This appendix is intended for sites in areas where COVID-19 has affected the workload of study sites, severe movement restrictions have been imposed, or where there is a risk to participants or site staff when attending visits at the site. The duration of these changes will be agreed upon between the site and sponsor/CRO and can be extended based on the local epidemic status.

10.7.3.2. Testing for COVID-19

Additional testing for COVID-19 beyond what is mandated by relevant local authorities and listed in the SoA (Section 1.3) is not required during the study. However, it is recommended that participants who develop COVID-19 symptoms during the study be tested again.

During the pandemic, the site staff should contact participants prior to each visit to inquire about COVID-19 symptoms (ie, fever, cough, sneezing, loss of taste/smell, difficulties breathing/chest tightness) and exposure to determine if it is safe for the participant to proceed with the visit as planned. If a participant tests positive for SARS-CoV-2 or has symptoms of COVID-19, he/she should not return to the site for visits until the investigator decides it is safe for the participant to return, based on local regulations and guidance from the site staff.

10.7.3.3. Study Protocol Changes

If the COVID-19 pandemic results in significant participant discontinuation, the sites may increase the recruitment of potential participants to replace the lost participants.

10.7.3.4. Critical Parameters to Be Collected During the Study

All assessments should be performed as indicated in the SoA (Section 1.3) if possible. In the event that some assessments cannot be performed due to the COVID-19 pandemic, the following critical parameters must be collected: all AE reporting, administration site reactions, SIB monitoring, IMP administration, who performed the administration, training and competency to perform self-administration, MG-ADL total score, and IgG levels from the first visit through day 29.

10.7.3.5. Mandatory Site Visits and Home Visits

All visits must be performed at the site if possible. If adaptations are required due to the COVID-19 pandemic, the following visits must be performed at the site if possible.

- screening visit
- all TP visits

- first follow-up visit on day 29
- EoS visit

All other visits may be performed by phone if necessary, and all activities that do not require the participant to be on site will be performed.

10.8. Appendix 8: Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

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- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

10.9. Appendix 9: Abbreviations and Definitions

10.9.1. Definitions

Enrolled: A participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Japanese participant: A participant whose parents and 4 grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of >10 years, and currently lives in Japan.

MG-ADL responder: A participant who shows a decrease of at least 2 points from baseline on the MG-ADL score for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last administration of IMP.

QMG responder: A participant who shows a decrease of at least 3 points from baseline on the QMG score for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last administration of IMP.

Randomized: An enrolled participant has been randomly assigned to a treatment arm.

10.9.2. Abbreviations

AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	acetylcholine receptor binding autoantibodies
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AUC	area under the serum concentration-time curve
AUEC	area under the effect curve
CIOMS	Council for International Organizations of Medical Sciences
CL	total clearance
CL/F	apparent total clearance
C_{max}	maximum concentration
C_{trough}	concentration observed predose
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease-2019
CRO	contract research organization

CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EoS	end of study
EQ-5D-5L	EuroQoL 5-Dimensions 5-Level
ER	emergency room
FcRn	neonatal Fc receptor
FSH	follicle-stimulating hormone
gMG	generalized myasthenia gravis
GCP	Good Clinical Practice
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IRR	injection and/or infusion-related reaction
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	immune thrombocytopenia
ITT	intention-to-treat
IV	intravenous
IVIg	intravenous immunoglobulin

MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	Myasthenia Gravis Quality of Life 15 item scale revised
mITT	modified intention-to-treat
NAb	neutralizing antibody
NMJ	neuromuscular junction
NCI	National Cancer Institute
NSID	nonsteroidal immunosuppressant
PD	pharmacodynamics
PH20	recombinant human hyaluronidase PH20 (rHuPH20)
PHQ	Patient Health Questionnaire
PK	pharmacokinetics
PLEX	plasma exchange
PPE	personal protective equipment
PR	atrioventricular node delay interval
QMG	Quantitative Myasthenia Gravis
QoL	quality of life
QRS	duration of ventricular depolarization
QT	total duration of ventricular depolarization
QTcF	rate-corrected QT intervals using Fridericia's formula
RR	time between heart beats
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	statistical analysis systems
SC	subcutaneous
SCIg	subcutaneous immunoglobulin
SIB	suicidal ideation and behavior
SoA	Schedule of Activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
WOCBP	women of childbearing potential

WONCBP	women of nonchildbearing potential

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