PROTOCOL: ARGX-113-2002

PROTOCOL TITLE:

A Long-term, Single-Arm, Open-label, Multicenter Phase 3 Study to Evaluate the Safety and Tolerability of Multiple Subcutaneous Injections of Efgartigimod PH20 SC in Patients With Generalized Myasthenia Gravis

SHORT TITLE:

Evaluating the Long-term Safety and Tolerability of Efgartigimod PH20 SC Administered Subcutaneously in Patients With Generalized Myasthenia Gravis

STUDY PHASE:

3

ACRONYM:

ADAPT^{SC+}

COMPOUND:

Efgartigimod

REGULATORY AGENCY IDENTIFIER NUMBER(S):

Registry	**ID**
IND	[redacted]
EUDRACT	2020-004086-38

SPONSOR NAME:

argenx BV

LEGAL REGISTERED ADDRESS:

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9052 Zwijnaarde (Ghent)
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Phone: +32 9 310 34 00
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**PRINCIPAL/
COORDINATING
INVESTIGATOR:**

[redacted]

SIGNATURE OF THE SPONSOR

Protocol Title: A Long-term, Single-Arm, Open-label, Multicenter Phase 3 Study to Evaluate the Safety and Tolerability of Multiple Subcutaneous Injections of Efgartigimod PH20 SC in Patients With Generalized Myasthenia Gravis

Protocol Number: ARGX 113 2002

Sponsor Signatory:

See appended signature page

[redacted], **MD, PhD**
Chief Medical Officer

Date

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read this protocol for study ARGX-113-2002.

Title: A Long-term, Single-Arm, Open-label, Multicenter Phase 3 Study to Evaluate the Safety and Tolerability of Multiple Subcutaneous Injections of Efgartigimod PH20 SC in Patients With Generalized Myasthenia Gravis

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Institution Address: (please handprint or type)	
Signature	
Date	

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must inform argenx within 24 hours. A copy of the SAE form must also be sent to the contract research organization (CRO)/argenx BV medical monitor using the details below.

Email: safety@argenx.com

Toll-free Fax: +1 833 874 7325

The following numbers are also available for urgent contact:

24-Hour Urgent Medical Helpline Number:

EMEA/APAC +44 1223 374 240

North America +1 800 201 8725

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Global protocol document history	Date
Protocol version 3.0	02 Feb 2023
Protocol version 2.0	10 May 2021
Protocol version 1.0	14 Dec 2020

Amendment 2 (02 Feb 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2991/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The overall rationale for this amendment is:

- to extend the study duration
- to reduce the frequency of assessments from the second year onward, and to reduce requirements for on-site visits when the participant does not need treatment
- to align with the established safety, efficacy, and PK/PD profile of efgartigimod, which will reduce the burden for the participants
- to add optional photograph monitoring of injection site reactions

Changes from the Germany-specific protocol v2.2 have also been included. This global protocol v3.0 supersedes the Germany-specific protocol v2.2. For considerations and amendment history specific to Germany, please refer to Section 10.8. Changes in this protocol amendment apply once approval is completed within the given country.

The protocol has also incorporated the content of administrative clarification letters. The major changes from protocol v2.0 compared with protocol v3.0 are summarized in the following table. Minor editorial changes are not summarized, including correction of typographical errors and formatting inconsistencies. Refer to Section 10.7.2 of the protocol for any undefined abbreviations.

Summary of Changes Between Protocol Version 2.0 and Protocol Version 3.0

Section and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities Section 8.8.2 [redacted] Section 10.6.3.4 Critical Parameters to Be Collected During the Study	A new SoA has been created for the second year onward, with fewer assessments. The footnotes in the year 1 SoA have also been modified to remove references to year 2, and the EoS visit has been removed from year 1. Reduction of efficacy and safety assessments and removal of PD, PK, and QoL assessments from the year 2 SoA (compared to year 1 SoA) includes: **MG-ADL**, **SIB risk monitoring:** removed assessment at visit $TP_nV2/3/4$ **PD, PK, [redacted], MG-QoL15r, EQ-5D-5L:** removed all visits **Safety laboratory tests, urinalysis**, **urine pregnancy test**, **vital signs, ECG, physical examination, immunogenicity:** only retained at TP_nV1, at every 5 visits for IP visits (starting with IP_nV5), at ET/SFU and EoS visit, and at UNS visit when considered necessary by the investigator References to "TP_nVn" have also been corrected to "TP_nVm," because "n" should refer to the treatment period number, and "m" should refer to the visit number.	**Efficacy/PD/PK:** Consistency in efficacy, PD, and PK of efgartigimod is well established (refer to the current IB). Therefore, the clinical assessments can be reduced and the collection of PD and PK samples can be removed from the second year onward. **Safety/immunogenicity:** A favorable benefit-risk profile of EFG in gMG patients has been established. Frequency of safety assessments will be adapted to align with the safety profile of efgartigimod and to reduce the burden on the participant. Pregnancy testing is also reduced in frequency because reproductive toxicity risk has been shown to be low (refer to the current IB).

Section and name	Description of change	Brief rationale
Section 4.1 Overall Design Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities	The total study duration has been extended. Participants will remain in the study for at least 1 year, until efgartigimod PH20 SC becomes commercially available or available through another continued access program for gMG, or until 31 Dec 2024, whichever comes first.	The study has been extended to provide prolonged access to IMP, to provide additional benefit for the participant and collect safety data beyond 2 years of exposure.
Section 8.3.7 AEs of Clinical Interest Section 2.3.1. Risk Assessment Section 8.2.7 Assessment of Injection Site	Section 8.3.7 has been added to define AEs of clinical interest, revise the definition of injection-site reaction (ISR), and include the option for photographic monitoring. Section 2.3.1 has been renamed and updated to align with Section 8.3.7. Former Section 8.2.7 was deleted because it was redundant to the new Section 8.3.7.	The definition of ISR was revised to clarify that injection-site reactions and injection-related reactions are AEs of clinical interest. ISR photographic monitoring is now included to allow collection of more ISR information.
Section 2.3.1, Table 3 Potential Risks and Mitigation Strategies	Risks and mitigation strategies for serious infection, injection-related reactions, and injection-site reactions have been updated; risks and mitigation strategies for teratogenicity/fetotoxicity have been deleted.	The safety information on potential risks and mitigation strategies has been updated.
Section 2 Introduction	The introduction, background, and benefit/risk assessment sections were updated to streamline the most recent information regarding efgartigimod studies and risks and benefits.	The efficacy and safety of efgartigimod has been established, and efgartigimod is approved in various regions. The introduction, background, and benefit/risk assessment sections have been updated to reflect this.

Section and name	Description of change	Brief rationale
Section 6.8.3 Prohibited Medications and Procedures	The language was updated on prohibited therapies that will result in participant discontinuation and prohibited activities during year 1 that will not require discontinuation.	The text was updated to clarify which prohibited therapies must result in participant discontinuation from the study, and which prohibited activities during year 1 do not require discontinuation from the study.
Section 7.2 Participant Discontinuation/Withdrawal From the Study	The following bullet point was added: "participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship."	The discontinuation requirement was added to ensure any participant receiving a malignancy diagnosis—whether recurrent or not—except basal cell carcinoma of the skin, permanently discontinues IMP.
Section 8.2.4 Electrocardiograms	The ECG instructions were revised to indicate that single 12-lead ECGs will be obtained predose on dosing days, using an ECG machine.	The ECG instructions have been simplified to align the protocol with the Data Transfer Agreement with the ECG vendor.
Section 10.1.3 Informed Consent Process	The language was updated to clarify that before signing the ICF, participants will be instructed not to participate in any other clinical study that involves a therapeutic intervention until the completion of the study.	Participants should no longer be excluded or discontinued for enrolling in another study not involving a therapeutic intervention. This change aligns with the protocol clarification letter dated 24 Aug 2021.
Section 10.6.3.3 Study Protocol Changes	The home nurse and home visit language was updated: • Added "if allowed per local requirement" to the sentence "A home nurse will be a qualified person from either the study site staff or a home health care vendor." • Removed "Mandatory site visits and home visits" section (formerly Section 10.7.3.5).	The language was updated to account for local requirements, to allow the home nurse to be either study site staff or staff from a home health care vendor, and to note that the use of a home nurse depends on regional availability.

Section and name	Description of change	Brief rationale
Section 10.2 Clinical Laboratory Tests Section 1.3 Schedule of Activities	Section 10.2.1 was removed, which included apolipoprotein B (apoB), lipoprotein A, fibrinogen, von Willebrand factor, d-dimer, and proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9).	Efgartigimod does not reduce albumin levels and has had no observed effect on cholesterol, high density lipoprotein, or low density lipoprotein levels. Therefore, the monitoring of factors influenced by changing lipid levels is not relevant. The removal of PCSK9 aligns with the protocol clarification letter dated 03 Feb 2022.
Section 11 References	The former Investigator's Brochure (IB) references 4 and 5 were removed; language was changed to "refer to current IBs" throughout.	The references were updated to remove outdated IBs.
Section 10.1.9 Study and Site Start and Closure	The following additional criteria for study termination were added: • An unexpected negative change to the benefit-risk profile of the IMP • Recommendation of termination by the DSMB • A necessary adjustment to the maximum insured sum for the study that is not possible • Regulatory agency and/or IRB/IEC approvals withdrawn	Criteria for study termination were added based on feedback from the ethics committee in Germany. These changes align with Germany-specific protocol v2.2.
Section 10.6 Appendix 6: Administrative Structure	Section 10.6. Appendix 6 was removed, including Table 4, List of Vendor Information.	Regulation (EU) No. 536/2014 does not require a list of the vendors in the protocol.
Section 5.1 Inclusion Criteria	Inclusion criterion 2a was revised to read as follows: "…Were discontinued from study treatment for reasons other than pregnancy or a life-threatening SAE. Receiving rescue therapy	The inclusion criterion was updated to clarify that a participant is eligible if they were discontinued due to an SAE that was not life-threatening. This revision aligns with the protocol clarification letter dated 01 Dec 2021.

Section and name	Description of change	Brief rationale
	is not exclusionary unless given in a response to a life-threatening situation."	
Section 4.1 Overall Design Section 1.3 Schedule of Activities (Table 1) Section 10.6.3.3 Study Protocol Changes	The language has been updated to clarify that the first and second visits of an IP, before the first TP and after a TP, must occur on-site.	The language was updated to align with the protocol clarification letter dated 03 Feb 2022.
Section 8.2.8.2 ADA Against rHuPH20 Section 1.3 Schedule of Activities	The language was updated to clarify that the baseline sample for ADA against recombinant human hyaluronidase PH20 (rHuPH20) will not be obtained until the first visit of the first TP (TP1V1), and that samples taken during the second year will only be analyzed if needed for safety purposes.	The language was updated to align with the protocol clarification letter dated 03 Feb 2022 and to clarify how samples will be used in the second year.
Section 8.3.7.2 Injection-Site Reaction	The section was updated to include the most frequently reported injection-site reactions and to update the routine precautionary procedures regarding injection-site reactions.	This text was updated to align with current company standards on injection-site monitoring.
Section 4.1 Overall Design Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 6.2.2 Handling Section 6.4 Study Intervention Compliance	The language in Section 4.1 was updated to specify that ≥2 visits are required for a participant or caregiver to be considered competent to administer efgartigimod PH20 SC at home. Cross-references to Section 4.1 have replaced detailed explanations in other sections.	The language was updated to align with the protocol clarification letter dated 03 Feb 2022.
Section 8.2.9 Vaccine Antibody Titers and PBMCs	The vaccination language has been updated to read as follows:	The language was updated to clarify the time points when additional blood samples may be needed if the participant receives a vaccination during the study.

Section and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities	"…the following samples are to be taken in case of vaccination: • The baseline serum sample can be taken at any moment before the vaccination is administered. This sample does not have to be taken at the baseline visit. • The second serum sample is to be taken at least 4 weeks after the vaccine has been administered. • A third serum sample is to be taken at the first IPnV1 that is at least 4 weeks after the vaccine has been given. In case the visits of the second and the third sample coincide, then only 1 sample is needed."	This change aligns with the protocol clarification letter dated 24 Aug 2021.

Section and name	Description of change	Brief rationale
Section 10.2 Clinical Laboratory Tests	Table 7 has been updated to include bilirubin (total and direct), gamma-glutamyl transferase (GGT [γ-GT]), C-reactive protein (CRP), lactate dehydrogenase (LDH), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Total protein, mean corpuscular hemoglobin (MCH), and urobilinogen were removed. The table was further updated as follows: • Added prothrombin time (PT) • Added coagulation panel label, which includes aPTT, PT, and INR • Updated "routine analysis" label to "routine urinalysis" • Updated "MV" to "MCV" (mean corpuscular volume) • Added "WBC count with differential" as a heading for basophils, eosinophils, lymphocytes, monocytes, and neutrophils • Added "RBC indices" as a heading for MCV and % reticulocytes • Added creatinine clearance to clinical chemistry	The table was updated to correct the unintentional removal and insertion of laboratory parameters in protocol v2.0 (10 May 2021). This change aligns with the protocol clarification letter dated 18 Jul 2022, and with the changes made in Germany-specific protocol v2.2. PT was added because the central lab analyzes PT as a part of the coagulation panel. Creatinine clearance was added to clarify that this measurement is required. Edits to the labeling were made for clarity.
Section 4.1 Overall Design Section 1.1 Synopsis Section 1.2 Schema	The 28-day restriction between treatment periods for year 2 onward was removed, and treatment	As treatment management aims at minimizing fluctuations in disease severity, some participants may benefit from earlier initiation of the subsequent treatment

Section and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities Section 4.3 Justification for Dose Section 6.5 Dose Modification Section 7.1.1 Temporary Discontinuation of Study Intervention	period labels were updated. The limit of 14 treatment periods was removed, and the number of weeks required for retreatment to occur was adjusted. All references to "treatment cycle" were changed to "treatment period" for clarity. Errors and unclear references to "IP_nVm" labeling have been corrected.	period. Changes were made to allow for collection of safety data in participants with cycles <50 days.
Section 6.7 Treatment of Overdose	The section was updated to define and differentiate overdose and medication error, and to describe the specific administration amounts and timeframes that constitute overdoses/medication errors.	The text was updated to clarify the difference between overdoses and medication errors that are specific to SC administration.
Section 6.4.2 Protocol Deviations	Language was removed that suggested approval from the sponsor is allowed for protocol deviations.	The sponsor does not approve or reject protocol deviations.
Section 6.2.3 Storage	Certificate of analysis and certificate of conformity were removed from required documents for the investigator.	The language was updated to align with required documents per GCP regulatory requirements.
Section 10.6.3.2 Testing for COVID-19	The COVID-19 testing requirements were updated to clarify that participants must test negative for SARS-CoV-2 and be symptom free to be (re)treated.	The language was updated to align with other parts of the text.
Section 1.1 Synopsis	"Overall Design" was updated to remove the requirement that participants be on current gMG therapy.	This requirement was removed because the current gMG therapy may be tapered per investigator discretion.

Section and name	Description of change	Brief rationale
Section 4.4 End of Study Definition	The end of study definition was updated to: "The end of the study is defined as the date of the last participant's last visit."	The text was updated to clarify that the end of the study is not related to whether a participant discontinues early.
Section 6.6 Continued Access to IMP After the End of the Study	The section was retitled and its text replaced with the following: "At the end of the study, argenx cannot guarantee continued access for participants but will comply with all local laws and regulations."	The language was updated to reflect the sponsor's updated policy for continued access to IMP.
Section 8.2.2 Physical Examinations	The following text was deleted: "Weight will be measured at study entry, at the ET/SFU visit, at the EoS visit, and at UNS visits."	The in-text reference to time points for weight measurement was removed because all respective time points are specified in the SoA.
Section 8.2.3 Vital Signs	The first paragraph of the section was edited to remove "…be measured in a semi-supine position after 5 minutes rest and will…"	This text was removed because it is redundant.
Section 8.2.7 Pregnancy Testing	The section was updated to refer to the SoA for the timing of urine pregnancy testing and to remove reference to serum pregnancy testing and testing entry criteria.	The text was updated to clarify when a urine pregnancy test should be used and to clarify that there is no screening visit in this study and no pregnancy serum testing.
1.1 Synopsis 1.3 Schedule of Activities	The language was updated to clarify that if a participant enters year 2 of the study during a TP, the remaining TP visits and subsequent IPnV1 must be completed according to the year 1 SoA.	The language was updated to provide instruction on which SoA applies if a participant transitions to year 2 during a TP.

Section and name	Description of change	Brief rationale
10.5.2.2 Male Contraception Section 5.1 Inclusion Criteria	The language has been updated to note that there is no requirement for male contraception.	The requirements were updated to align with most the recent version of the efgartigimod IB.
Section 5.2 Exclusion Criteria	Criterion 3a has been updated to indicate that medical conditions are relative to rollover, not screening.	This study does not have a screening visit, so medical condition requirements are relative to rollover.
Section 1.2 Schema	Figure 2 was updated to align the visit labels with Figure 1.	Visit numbers in Figure 2 were clarified.
Signature of the Sponsor	The sponsor signatory has been updated to [redacted] MD, PhD.	The signature page was updated to reflect the sponsor's current chief medical officer.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Long-term, Single-Arm, Open-label, Multicenter Phase 3 Study to Evaluate the Safety and Tolerability of Multiple Subcutaneous Injections of Efgartigimod PH20 SC in Patients With Generalized Myasthenia Gravis

Brief Title: Evaluating the Long-term Safety and Tolerability of Efgartigimod PH20 SC Administered Subcutaneously in Patients With Generalized Myasthenia Gravis

Rationale:

The aim is to evaluate the long-term safety and tolerability of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC) (efgartigimod PH20 SC) and its efficacy in patients with generalized myasthenia gravis (gMG).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of efgartigimod PH20 SC in participants with gMG	• Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs) and AEs of special interest (AESIs) and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram results
Secondary	
• To evaluate the impact of efgartigimod PH20 SC on disease severity	• Myasthenia Gravis Activities of Daily Living (MG-ADL) total score changes from baseline and cycle baseline over time by cycle
• To evaluate the effect of efgartigimod PH20 SC on pharmacodynamics (PD)	• Percentage reduction in levels of total immunoglobulin G (IgG) from baseline and cycle baseline over time by cycle • Percentage reduction of anti-acetylcholine receptor antibodies (AChR-Ab) from baseline and cycle baseline over time by cycle in AChR-Ab seropositive participants
• To evaluate the PK of efgartigimod PH20 SC	• Efgartigimod serum concentrations

• To evaluate the immunogenicity of efgartigimod PH20 SC	• Incidence and prevalence of anti-drug antibodies (ADAs) to efgartigimod over time • Incidence and prevalence of neutralizing antibodies (NAbs) against efgartigimod over time • Incidence and prevalence of ADAs to rHuPH20 over time • Incidence and prevalence of NAbs against rHuPH20 over time
• To evaluate the impact of efgartigimod PH20 SC on the quality of life (QoL) of the participants	• Changes in total Myasthenia Gravis Quality of Life Questionnaire (15-item scale revised) (MG-QoL15r) from baseline and cycle baseline by cycle • Changes in EuroQoL 5-Dimensions 5-Level (EQ-5D-5L) visual analog scale (VAS) score from baseline and cycle baseline over time by cycle • EQ-5D-5L responses to 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, anxiety/depression) over time by cycle
• To evaluate feasibility of self-administration of efgartigimod PH20 SC	• Number and percentage of participants who performed self-administration at home over time by cycle • Number and percentage of caregivers who administered the injection to the participant at home over time by cycle • Number of training visits needed for the participant or caregiver to be competent to start administering efgartigimod PH20 SC • Number and percentage of self- or caregiver-supported study drug administration among all study treatment visits at home

Exploratory	
• [redacted]	• [redacted] • [redacted]

Overall Design:

ARGX-113-2002 is an open-label, multicenter, long-term safety study in patients with gMG, including both anti-acetylcholine receptor antibody (AChR-Ab) seropositive and seronegative participants. Participants will enter the study from either study ARGX-113-2001 or from study ARGX-113-1705. Once a participant has clinical need of retreatment, they will receive efgartigimod PH20 SC 1000 mg every 7 days (q7d) for a total of 4 injections in a treatment period (TP). Depending on the clinical effect, participants may be retreated as needed using a variable number of TPs. An independent Data and 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 evaluate the long-term safety and tolerability of efgartigimod PH20 SC 1000 mg, and the clinical efficacy, PD, pharmacokinetics (PK), immunogenicity, impact on the QoL of the participants, treatment satisfaction, and administration method preference, and the feasibility of self- and caregiver-supported administration of the SC injection. PD and PK will only be measured and assessed through the first year.

Study details include:

- Study duration and treatment duration: from the participant's first visit in this study until, at the latest, 31 Dec 2024
- Treatment period and intertreatment period (IP):
  - Year 1: 3-week TPs of once weekly injections, repeated as needed with at least 28 days between TPs
  - Year 2 onward: 3-week TPs of once weekly injections. It is recommended to have IPs of at least 28 days, but a subsequent treatment period can be administered earlier based on clinical evaluation at the discretion of the investigator. A minimal interval of 7 days after the last investigational medicinal product (IMP) administration of the previous cycle must be maintained.
- Study Assessments and Procedures:

  - Year 1: total levels of immunoglobulin G (IgG), AChR-Ab levels, MG-ADL
  - Year 2: MG-ADL
- Visit frequency:
  - Year 1: every week during the TPs. Then, the first IP visit is 1 week after the last TP visit, then every 21 days (+7 days) until the participant is in need of retreatment
  - Year 2 onward: every week during the TPs. Then, the first IP visit, if applicable, is 1 week after the last TP visit, and then every 21 days (**+7** days). The new TP can start as soon as 1 week after the last TP, depending on when the participant is in need of retreatment.

Number of Participants:

Up to 201 participants may be enrolled from the antecedent studies ARGX-113-2001 and ARGX-113-1705. See Section 9.2.

Note: "Enrolled" means a participant's agreement to enter 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.

Intervention Groups and Duration:

The study spans the following study periods:

- treatment period (TP):
  - All years: 3 weeks, repeated as needed based on clinical evaluation by the investigator
  - If a participant enters year 2 of the study during a TP, the remaining TP visits and subsequent IP_nV1 must be completed according to the Year 1 SoA (refer to Table 1).
- intertreatment period (IP):
  - Year 1: at least 28 days between TPs
  - Year 2 onward: recommended to have IPs of at least 28 days, but a subsequent TP can be administered earlier based on clinical evaluation at the discretion of the investigator. A minimal interval of 7 days after the last IMP administration of previous cycle must be maintained.

Eligible participants will enter the study on their last visit of the antecedent study, ARGX-113-2001 or ARGX-113-1705. If they are in need of retreatment, the participants will start with a TP. A TP will consist of an injection of efgartigimod PH20 SC 1000 mg q7d for a total of 4 injections. If the participants are not in need of retreatment, they will start with an IP (visit IP_0V1). Participants or their caregivers will be trained to perform the injection and will be allowed to perform the injection when they are competent to do so. Caregiver-supported or

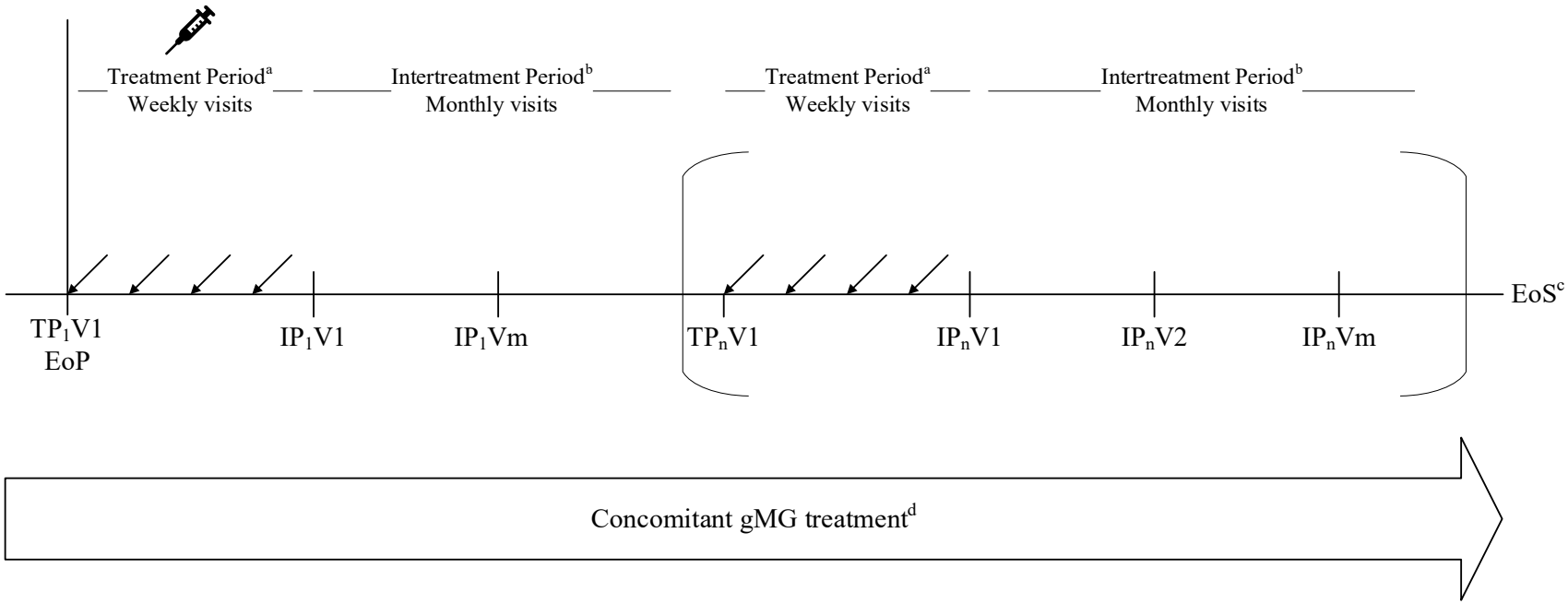
self-administration can be performed at the site or at home, based on the participant's preference. Participants will be discontinued from the study if it is in their best interest, as determined by the investigator or sponsor.

Participants will remain in the study for at least 1 year, until efgartigimod PH20 SC becomes commercially available, available through another continued access program for gMG, or until 31 Dec 2024, whichever comes first.

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

1.2. Schema

Figure 1: Schema for Participants in Need of Retreatment at Study Entry



EoP=end of study/early discontinuation visit for antecedent studies ARGX-113-2001 or ARGX-113-1705; EoS=end of study; gMG=generalized myasthenia gravis; IMP=investigational medicinal product; IP_nVm=intertreatment period (period number) visit (visit number); PH20=recombinant human hyaluronidase PH20 (rHuPH20); q7d=every 7 days; SC=subcutaneous(ly); SoA=schedule of activities; TP=treatment period; TP_nVm=treatment period (period number) visit (visit number)

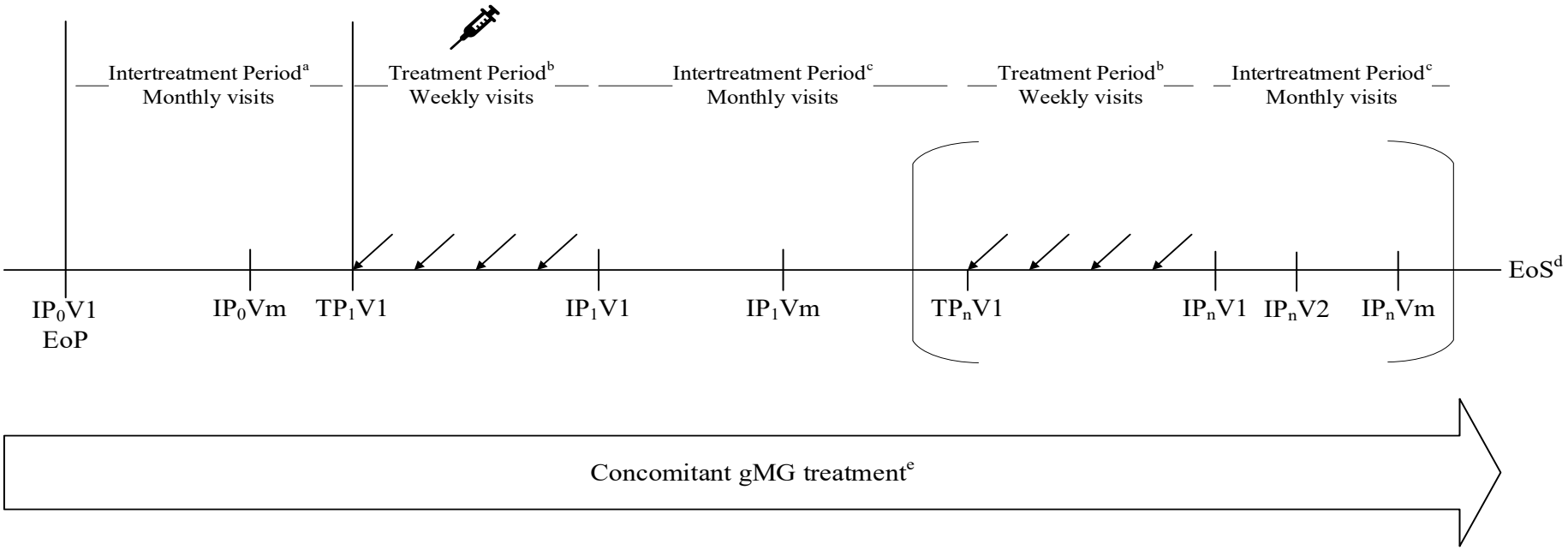
[a] Participants will receive efgartigimod PH20 SC 1000 mg q7d for a total of 4 injections in a TP. A new TP can be started if the participant is in need of retreatment as determined by the investigator, however during the first year, at least 28 days must have elapsed since the last dose of efgartigimod. During the second year onward, it is recommended to have at least 28 days between TPs. However, a subsequent treatment period can be administered earlier based on clinical evaluation at the discretion of the investigator, with a minimum interval of 7 days after the last IMP administration. In case of retreatment, there must be at least 4 weeks left in the study for the participant, so that a full TP and the EoS visit can be performed.

[b] For the visit schedule, see the SoA (Section 1.3).

[c] Participants will remain in the study for at least 1 year, until efgartigimod PH20 SC becomes commercially available or available through another continued access program for gMG, or until 31 Dec 2024, whichever comes first.

[d] Dose reduction or changes to the dose are allowed as described in Section 6.8.2. Concomitant gMG treatment can be tapered completely.

Figure 2: Schema for Participants Not in Need of Retreatment at Study Entry



EoP=end of study/early discontinuation visit for antecedent studies ARGX-113-2001 or ARGX-113-1705; EoS=end of study; gMG=generalized myasthenia gravis; IMP=investigational medicinal product; IP_nVm=intertreatment period (period number) visit (visit number); PH20=recombinant human hyaluronidase PH20 (rHuPH20); q7d=every 7 days; SoA=schedule of activities; TP=treatment period; TP_nVm=treatment period (period number) visit (visit number)

[a] During the intertreatment period, visits will occur every 21 days. TP_1V1 will occur when a participant is eligible for retreatment.

[b] Participants will receive efgartigimod PH20 SC 1000 mg q7d for a total of 4 injections in a TP. A new TP can be started if the participant is in need of retreatment as determined by the investigator, however during the first year, at least 28 days must have elapsed since the last dose of efgartigimod. During the second year onward, it is recommended to have at least 28 days between TPs. However, a subsequent treatment period can be administered earlier based on clinical evaluation at the discretion of the investigator, with a minimum interval of 7 days after the last IMP administration. In case of retreatment, there must be at least 4 weeks left in the study for the participant, so that a full TP and the EoS visit can be performed.

[c] For the visit schedule, see the SoA (Section 1.3).

[d] Participants will remain in the study for at least 1 year, until efgartigimod PH20 SC becomes commercially available or available through another continued access program for gMG, or until 31 Dec 2024, whichever comes first.

[e] Dose reduction or changes to the dose are allowed as described in Section 6.8.2. Concomitant gMG treatment can be tapered completely.

1.3. Schedule of Activities

Table 1: Schedule of Activities for Year 1

	Treatment Period						Intertreatment Period			
Visit Type	**TP_nV1[a,b]**	**PK1[b,c]**	**TP_nV2**	**TP_nV3**	**TP_nV4**	**PK2[b,c]**	**IP_nV1[b]**	**IP_0V1[a,b]/ IP_nVm[d]**	**ET/SFU[b,e]**	**UNS[f]**
Study Day (Visit Window)	**A**	**A+2 (±1)**	**A+7 (±2)**	**A+14 (±2)**	**A+21 (±2)**	**A+23 (±1)**	**A+28 (±2)**	**Y+21 (+7)**	**NA**	**NA**
Informed consent	X[g]							X[g]		
Inclusion/ exclusion criteria	X[g]							X[g]		
Demographic characteristics	X[g]							X[g]		
Weight	X[g]							X[g]	X	X
MG-ADL[h]	X		X[i]	X[i]	X[i]		X	X[i]	X	X
MG-QoL15r	X		X[i]	X[i]	X[i]		X	X[i]	X	X
EQ-5D-5L	X						X	X[i]	X	X
[redacted]	[redacted]									
[redacted]	[redacted]									
SIB risk monitoring[m]	X		X[i]	X[i]	X[i]		X	X[i]	X	X
Single 12-lead ECG	X						X	X	X	X
Physical examination	X						X	X	X	X

Visit Type	Treatment Period						Intertreatment Period			
	TP_nV1[a,b]	**PK1**[b,c]	**TP_nV2**	**TP_nV3**	**TP_nV4**	**PK2**[b,c]	**IP_nV1**[b]	**IP_0V1**[a,b]/ **IP_nVm**[d]	**ET/SFU**[b,e]	**UNS**[f]
Study Day (Visit Window)	**A**	**A+2 (±1)**	**A+7 (±2)**	**A+14 (±2)**	**A+21 (±2)**	**A+23 (±1)**	**A+28 (±2)**	**Y+21 (+7)**	**NA**	**NA**
Vital signs	X						X	X	X	X
Safety laboratory tests[n]	X						X	X	X	X
Vaccination antibody titers and PBMCs[o]	(X)		(X)	(X)	(X)		(X)	(X)	(X)	X
Immunogenicity[p]	X						X	X	X	X
Pharmaco-dynamics[q]	X						X	X	X	X
Pharmacokinetics	X[r]	X				X	X		X	X
SARS-CoV-2 test[s]										X
Urinalysis	X						X	X	X	X
Urine pregnancy test[t]	X						X	X	X	X
Efgartigimod PH20 SC administration training[u]	X		(X)	(X)	(X)		X	(X)		X
Efgartigimod PH20 SC administration[v]	X		X[i]	X[i]	X[i]					

Visit Type	Treatment Period						Intertreatment Period		ET/SFU[b,e]	UNS[f]
	TP_nV1[a,b]	PK1[b,c]	TP_nV2	TP_nV3	TP_nV4	PK2[b,c]	IP_nV1[b]	IP_0V1[a,b]/ IP_nVm[d]		
Study Day (Visit Window)	**A**	**A+2 (±1)**	**A+7 (±2)**	**A+14 (±2)**	**A+21 (±2)**	**A+23 (±1)**	**A+28 (±2)**	**Y+21 (+7)**	**NA**	**NA**
Administration compliance monitoring[w]	Continuous monitoring[i]									
Assessment of injection site[x]	Continuous monitoring[i]									
Hospitalization monitoring[y]	Continuous monitoring[i]									
Adverse events[y]	Continuous monitoring[i]									
Prior/concomitant therapy and procedures[y]	Continuous monitoring[i]									

A=day 1 of a TP; AChR-Ab=anti-acetylcholine receptor antibody; ADA=antidrug antibodies; AE=adverse event; eCRF=electronic case report form; ECG=electrocardiogram; ET=end of treatment; FSH=follicle-stimulating hormone; ICF=informed consent form; IgG =immunoglobulin G; IMP=investigational medicinal product; IP=intertreatment period; IP_nVm=IP (period number) visit (visit number); [redacted]; MG-ADL=Myasthenia Gravis Activities of Daily Living; MG-QoL15r=Myasthenia Gravis Quality of Life 15 item scale revised; NA=not applicable; NAb=neutralizing antibody; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamics; PH20=recombinant human hyaluronidase PH20 (rHuPH20); PHQ-9=9-item Patient Health Questionnaire; PK=pharmacokinetics; PK1 and PK2=additional pharmacokinetic sample visits for subset of participants; SC=subcutaneous(ly); SFU=safety follow-up; SIB=Suicidal Ideation and Behavior; SoA=schedule of activities; TP=treatment period; TP_nV_m=TP (period number) visit (visit number); [redacted]; UNS=unscheduled; (X)=optional activity, only done under specified conditions; Y=previous IP visit

Note: All activities will be performed predose on dosing days, unless otherwise indicated.

[a] The transition from the antecedent studies ARGX-113-1705 or ARGX-113-2001, to study ARGX-113-2002, can either be IP_0V1 or TP_1V1, depending on the need for retreatment. The first visit of study ARGX-113-2002 will always coincide with the last visit from studies ARGX-113-2001 or ARGX-113-1705. Overlapping activities performed for the last visit of these antecedent studies will not be repeated for the first visit of ARGX-113-2002.

[b] This visit must always be performed at the site. All other visits can be performed by phone if IMP administration occurs at home.

[c] These are optional visits to collect additional PK samples from consenting participants. These additional visits can only be performed when all of the injections of that treatment period are given at the site. Sampling will only be performed during a participant's first and/or second treatment periods that start during the first year.

[d] These IP visits will occur every 21 days. The visit denominator ("m") will start at 2 for each IP after a TP. At each of these IP visits performed on-site, an evaluation of the need for retreatment will be done prior to performing any activities so that only activities listed for IP_nVm or TP_nV1 are performed, respectively. The first visit of an IP after a TP, called IP_nV1, must occur on-site. The second IP visit (IP_nV2) will also be on-site. Subsequent visits may alternate between telephone and on-site visits. During an IP, consecutive telephone visits are not allowed, except in exceptional circumstances caused by the COVID-19 pandemic and after approval by the sponsor and/or the CRO.

[e] For participants who discontinue early from the study, the activities will depend on the visit at which the participant had to discontinue. Participants who discontinue early from the study at either a TP visit or an IP visit should perform planned activities for the ET visit if 49 (±2 days) days has not elapsed since the last dose of efgartigimod. These participants will not receive any further administration of efgartigimod PH20 SC during the study and will return for the SFU visit 49 ±2 days after the last dose administration. If 49 ±2 days has already elapsed since the last administration of efgartigimod PH20 SC, then this visit becomes the SFU visit and the SFU visit activities must be performed. Participants who discontinue early from the study between visits should perform the SFU visit at least 49 ±2 days after the last dose administration. If 49 ±2 days has already elapsed since the last administration of efgartigimod, then the SFU visit will be planned as soon as possible.

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

[g] These activities are only performed at study entry.

[h] It is recommended to perform the MG-ADL scale prior to all other activities.

[i] When a visit is performed by phone, only these activities must be performed.

[j] [redacted]

[k] [redacted]

[l] [redacted]

[m] The SIB Risk Monitoring assessment is based on question 9 of the PHQ-9.

[n] Blood samples for clinical laboratory (hematology/clinical chemistry/coagulation panel and FSH, if applicable) safety assessments will be collected. See Section 10.2. Participants will need to be fasted for each on-site visit at which safety laboratory assessments are collected. Fasted is defined as no food or drink at least 8 hours prior to each sampling. Permitted medications that the participant normally takes can be taken as usual before a visit.

[o] Additional blood samples (serum/PBMC) may need to be taken for additional/optional/future/vaccination research if the participant consents. If a participant who consents to this additional sampling receives a vaccination during the study, samples referred to in Section 8.2.9 should be taken. The closest visit that is at least 4 weeks after the vaccine was administered may be used. If this visit does not coincide with IP_nV1, then another sample will also be taken at this visit. Serum samples only need to be taken when a vaccination is planned or after a vaccination has occurred. In addition, a whole-blood sample to isolate PBMCs will be collected at study entry and then approximately every 3 months throughout the study during a scheduled on-site visit, regardless of the vaccines a participant has received.

[p] Titers of ADA and the presence of NAbs against efgartigimod will be measured in serum. Blood samples for plasma titer levels of ADA and NAbs against rHuPH20 will also be taken. A titer for ADA and the presence of NAbs against PH20 must be measured at the first visit of the first TP (TP_1V1) for participants coming from study ARGX-113-1705 and for participants coming from study ARGX-113-2001 who received efgartigimod IV. If no sample is taken, the reason will be recorded. The baseline sample for ADA against rHuPH20 will not be obtained until TP_1V1.

[q] The PD assessments comprises levels of total IgG, and autoantibody levels (AChR-Ab levels for AChR-Ab positive participants).

[r] The PK assessments will only be taken at TP_1V1.

[s] A nasopharyngeal swab will be performed to sample nasal and throat mucosal cells. Participants should only be tested for SARS-CoV-2 if they have symptoms of COVID-19 or if they were in contact with a person who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements. Participants may be retested as needed. See Section 10.6.

[t] Only for women of childbearing potential. See Section 8.2.7 and Section 10.5.1.

[u] Participants who have not previously self-administered efgartigimod PH20 SC in study ARGX-113-2001 will be instructed on self-administration as of TP_1V1 or IP_0V1 in study ARGX-113-2002. Training can continue until the participant or caregiver is ready to administer efgartigimod PH20 SC to the satisfaction of the site staff (a minimum of 1 visit). The participant or caregiver will then perform an administration under the supervision of site staff. Therefore, a minimum of 2 visits is required for a participant or caregiver to be considered competent to administer efgartigimod PH20 SC at home. Caregivers must sign the ICF before being trained in IMP administration. (X) indicates that this activity is optional and can only be performed on-site. At every on-site visit, the study staff must review the administration log and patient diary with the participant.

[v] The first dose administration of all TPs must be performed on-site, even if the dose is self-administered. Subsequent administrations in any TP may be performed at home, if the participant or caregiver has been trained and is competent to perform IMP administration. Participants or caregivers who were competent to administer efgartigimod PH20 SC in study ARGX-113-2001 may continue administration during study ARGX-113-2002 and may perform all but the first administration of a TP at home. For participants who have not previously received efgartigimod PH20 SC, self-administration or caregiver-supported self-administration can begin during the first TP if the participant or caregiver is trained and capable, but all these administrations must still be performed on-site under supervision by the site staff. During subsequent TPs, administration for visits 2, 3, and 4 may be performed at home. When IMP administration is performed at home, the associated visit will be performed by phone.

[w] When administration is performed at home, participant compliance with the efgartigimod PH20 SC dosing and administration schedule will be assessed by direct questioning at each visit. Any deviations from the planned dosage must be recorded. See Section 6.4.

[x] When a participant is not on-site, they must record any observed injection site reaction in the patient diary. The investigator will evaluate all reported injection site reactions and decide whether the site reaction is classified and reported as an AE.

[y] Adverse events (including ongoing AEs from the antecedent studies), use of concomitant therapies, use of rescue therapy, medical procedures performed on the participants, and hospitalizations will be collected from ICF signature until the last study-related activity. All available vaccination history for participants rolling over from ARGX-113-1705 should be recorded in the eCRF. All vaccines received during the study should be recorded as concomitant medication. See Section 6.8 and Section 8.3.

Table 2: Schedule of Activities for Year 2 Onward

Visit Type	Treatment Period		Intertreatment Period[a]		ET/EoS/SFU[b,c,d]	UNS[e]
	TP_nV1[b,c]	$TP_nV2/V3/V4$	IP_nV1	IP_nVm[b,c]		
Study Day (Visit Window)	**A**	**A+7/14/21 (±2)**	**A+28 (±2)**	**Y+21 (+7)**	**NA**	**NA**
MG-ADL[f]	X		X	X	X	X
SIB risk monitoring[g]	X		X	X	X	X
Single 12-lead ECG	X			X[h]	X	X
Vital signs	X			X[h]	X	X
Physical examination	X			X[h]	X	X
Weight					X	X
Safety laboratory tests[i]	X			X[h]	X	X
Vaccination antibody titers and PBMCs[j]	(X)	(X)	(X)	(X)	(X)	X
Immunogenicity[k]	X			X[h]	X	X
SARS-CoV-2 test[l]						X
Urinalysis	X			X[h]	X	X
Urine pregnancy test[m]	X			X[h]	X	X
Efgartigimod PH20 SC administration training[n]	(X)	(X)	(X)	(X)	(X)	X
Efgartigimod PH20 SC administration[o]	X	X				
Administration compliance monitoring[p]	Continuous monitoring					
Assessment of injection site[q]	Continuous monitoring					
Hospitalization monitoring[r]	Continuous monitoring					

Visit Type	Treatment Period		Intertreatment Period[a]		ET/EoS/SFU[b,c,d]	UNS[e]
	TP_nV1[b,c]	$TP_nV2/V3/V4$	IP_nV1	IP_nVm[b,c]		
Study Day (Visit Window)	**A**	**A+7/14/21 (±2)**	**A+28 (±2)**	**Y+21 (+7)**	**NA**	**NA**
Adverse events[r]	Continuous monitoring					
Prior/concomitant therapy and procedures[r]	Continuous monitoring					

A=day 1 of a TP; ADA=antidrug antibodies; AE=adverse event; eCRF=electronic case report form; ECG=electrocardiogram; EoS=end of study; ET=end of treatment; FSH=follicle-stimulating hormone; gMG=generalized myasthenia gravis; ICF=informed consent form; IMP=investigational medicinal product; IP=intertreatment period; IP_nVm=IP (period number) visit (visit number); MG-ADL=Myasthenia Gravis Activities of Daily Living; NA=not applicable; NAb=neutralizing antibody; PBMC=peripheral blood mononuclear cell; PH20=recombinant human hyaluronidase PH20 (rHuPH20); PHQ-9=9-item Patient Health Questionnaire; SC=subcutaneous(ly); SFU=safety follow-up; SIB=Suicidal Ideation and Behavior; SoA=schedule of activities; TP=treatment period; TP_nVm=TP (period number) visit (visit number); UNS=unscheduled; (X)=optional activity, only done under specified conditions; Y=previous IP period visit
Note: All activities will be performed predose on dosing days, unless otherwise indicated. If a participant enters year 2 of the study during a TP, the remaining TP visits and subsequent IPnV1 must be completed according to the year 1 SoA (refer to Table 1).

[a] IPnV1 can become a TPn+1V1 if there are at least 7 days past the last IMP administration in the previous TP, and the participant is in need of retreatment. All IPnVm visits may also become a new TP, if the investigator determines there is a need for retreatment. The need for retreatment will be assessed prior to performing any activities, so that only activities listed for IPnV1/m or TPn+1V1 are performed, respectively. The visit denominator ("m") will start at 2 for each IP after a TP.

[b] Participants will remain in the study for at least 1 year, until efgartigimod PH20 SC becomes commercially available or available through another continued access program for gMG, or until 31 Dec 2024, whichever comes first.

[c] On-site visits are required for TPnV1, for IPnV5/10/15, etc, (ie, every 5 visits), and for ET, EoS, and SFU visits. All other visits in Table 2 can be performed by phone, including TPnV2/3/4 in case of IMP home administration.

[d] For participants who discontinue early from the study, the activities will depend on the visit at which the participant had to discontinue. Participants who discontinue early from the study at either a TP visit or an IP visit should perform planned activities for the ET visit if 49 (±2 days) days has not elapsed since the last dose of efgartigimod. These participants will not receive any further administration of efgartigimod PH20 SC during the study and will return for the SFU visit 49 ±2 days after the last dose administration. If 49 ±2 days has already elapsed since the last administration of efgartigimod PH20 SC, then this visit becomes the SFU visit and the SFU visit activities must be performed. Participants who discontinue early from the study between visits should perform the SFU visit at least 49 ±2 days after the last dose administration. If 49 ±2 days has already elapsed since the last administration of efgartigimod, then the SFU visit will be planned as soon as possible.

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

[f] It is recommended to perform the MG-ADL scale prior to all other activities.

[g] The SIB Risk Monitoring assessment is based on question 9 of the PHQ-9.

[h] These assessments will only be performed every 5 visits (IPnV5, IPnV10, etc).

[i] Blood samples for clinical laboratory (hematology/clinical chemistry/coagulation panel and FSH, if applicable) safety assessments will be collected. See Section 10.2. Participants will need to be fasted for each on-site visit at which safety laboratory assessments are collected. Fasted is defined as no food or drink at least 8 hours prior to each sampling. Permitted medications that the participant normally takes can be taken as usual before a visit.

[j] Additional blood samples (serum/PBMC) may need to be taken for additional/optional/future/vaccination research if the participant consents. If a participant who consents to this additional sampling receives a vaccination during the study, samples referred to in Section 8.2.9 should be taken. The closest visit that is at least 4 weeks after the vaccine was administered may be used. If this visit does not coincide with IPnV1, then another sample will also be taken at this visit. Serum samples only need to be taken when a vaccination is planned or after a vaccination has occurred. In addition, a whole-blood sample to isolate PBMCs will be collected at study entry and then approximately every 3 months throughout the study during a scheduled on-site visit, regardless of the vaccines a participant has received.

[k] Titers of ADA and the presence of NAbs against efgartigimod will be measured in serum. Blood samples for plasma titer levels of ADA and NAbs against rHuPH20 will also be taken, but these will only be analyzed if needed for safety purposes.

[l] A nasopharyngeal swab will be performed to sample nasal and throat mucosal cells. Participants should only be tested for SARS-CoV-2 if they have symptoms of COVID-19 or if they were in contact with a person who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements. Participants may be retested as needed. See Section 10.6.

[m] This activity is only for women of childbearing potential. See Section 10.5.2.1.

[n] Training can continue until the participant or caregiver is ready to administer efgartigimod PH20 SC, to the satisfaction of the site staff (a minimum of 1 visit) before performing an administration under the supervision of site staff. Therefore, a minimum of 2 visits is required for a participant or caregiver to be considered competent to administer efgartigimod PH20 SC at home. Caregivers must sign the ICF before being trained in IMP administration.

[o] The first dose administration of all TPs (TPnV1) must be performed on-site, even if the dose is self-administered or administered by the caregiver. Subsequent administrations in any TP (TPnV2/3/4) may be performed at home, if the participant or caregiver has been trained and is competent to perform IMP administration. When IMP administration is performed at home, the associated visit will be performed by phone.

[p] When administration is performed at home, participant compliance with the efgartigimod PH20 SC dosing and administration schedule will be assessed by direct questioning at each phone visit. Any deviations from the planned dosage must be recorded. See Section 6.4.

[q] When a participant is not on-site, they must record any observed injection site reaction in the patient diary. The investigator will evaluate all reported injection site reactions and decide whether the site reaction is classified and reported as an AE.

[r] Adverse events (including ongoing AEs from the antecedent studies), use of concomitant therapies, use of rescue therapy, medical procedures performed on the participants, and hospitalizations will be collected from ICF signature until the last study-related activity. All vaccines received during the study should be recorded as concomitant medication. 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 neonatal Fc receptor (FcRn), developed for the treatment of generalized myasthenia gravis (gMG). Efgartigimod alfa IV (VYVGART) received regulatory approval in various jurisdictions for patients with gMG. The subject of this protocol is the SC formulation of efgartigimod, referred to as efgartigimod PH20 SC.

2.1. Study Rationale

The aim is to evaluate the long-term safety and tolerability of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC) (efgartigimod PH20 SC) and its efficacy in patients with gMG. As the SC formulation allows for self-administration, the study will explore the feasibility of self-administration and caregiver-supported administration, the impact of efgartigimod PH20 SC on quality of life (QoL), treatment satisfaction, and mode of administration preference.

The incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), vital signs, and laboratory assessments of participants receiving efgartigimod PH20 SC 1000 mg will be evaluated over time, as per the primary objective. The SC formulation includes 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 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 results in degradation of 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, 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.

The efficacy of efgartigimod IV based on the percentage of MG-ADL responders was demonstrated against placebo in study ARGX-113-1704. Further, there was a strong association between total IgG and AChR-Ab reductions and clinical response, as measured by the percentage of MG-ADL responders. This strong association was used to bridge from efgartigimod IV to efgartigimod PH20 SC in study ARGX-113-2001. This study showed noninferiority of the pharmacodynamic effect (as measured by IgG percent reduction at week 4) of efgartigimod PH20 SC 1000 mg compared with efgartigimod IV 10 mg/kg in participants with gMG after 1 treatment cycle of 4 weekly administrations.

Given efgartigimod's mechanism of action of reducing IgG levels, the strong association between total IgG reduction and clinical response in patients with gMG, the SC formulation of efgartigimod PH20 SC may provide an alternative to efgartigimod 10 mg/kg IV, giving patients with gMG treatment optionality and flexibility.

A detailed description of the chemistry, pharmacology, efficacy, and safety of efgartigimod is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of efgartigimod PH20 SC is provided in the current IB.

2.3.1. Risk Assessment

Overall, available data confirm that efgartigimod PH20 SC has been well tolerated across studies in different indications and has an acceptable safety profile.

Table 3: Potential Risks and Mitigation Strategies

Potential Clinically Significant Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk for infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.3.6). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.
Injection-related reactions	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions.	Monitor participants during administration and for 30 minutes thereafter for clinical signs and symptoms of injection-related reactions. Injection-related reactions are considered AEs of clinical interest (Section 8.3.7).
Injection-site reactions	Most AEs have been mild, transient injection-site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection-site reactions occurring less frequently include burning, erythema, pain, and numbness. Mild to moderate headache is commonly reported. Localized injection-site reactions were observed in studies of efgartigimod with PH20 administered SC.	Continuously monitor participants for injection-site reactions. Injection-site reactions are considered AEs of clinical interest (Section 8.3.7).

AE=adverse event; AESI=adverse event of special interest; IgG=immunoglobulin G; IMP=investigational medicinal product; PH20=recombinant human hyaluronidase PH20 (rHuPH20); SC=subcutaneous(ly)

2.3.2. Overall Benefit-Risk Conclusion

More detailed information about the known and expected benefits and risks of efgartigimod PH20 SC and reasonably expected AEs can be found in the current version of the IB.

3. OBJECTIVES AND ENDPOINTS

Table 4: Study ARGX-113-2002 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the long-term safety and tolerability of efgartigimod PH20 SC in participants with gMG	• Incidence and severity of AEs, incidence of SAEs, and AEs of special interest (AESIs), and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram results
Secondary	
• To evaluate the impact of efgartigimod PH20 SC on disease severity	• Myasthenia Gravis Activities of Daily Living (MG-ADL) total score changes from baseline and cycle baseline over time by cycle
• To evaluate the effect of efgartigimod PH20 SC on PD	• Percentage reduction in levels of total immunoglobulin G (IgG) from baseline and cycle baseline over time by cycle • Percentage reduction of anti-acetylcholine receptor antibodies (AChR-Ab) from baseline and cycle baseline over time by cycle in AChR-Ab seropositive participants
• To evaluate the PK of efgartigimod PH20 SC	• Efgartigimod serum concentrations
• To evaluate the immunogenicity of efgartigimod PH20 SC	• Incidence and prevalence of anti-drug antibodies (ADAs) to efgartigimod over time • Incidence and prevalence of neutralizing antibodies (NAbs) against efgartigimod over time • Incidence and prevalence of ADAs to rHuPH20 over time • Incidence and prevalence of NAbs against rHuPH20 over time

• To evaluate the impact of efgartigimod PH20 SC on the QoL of the participants	• Changes in total Myasthenia Gravis Quality of Life Questionnaire (15-item scale revised) (MG-QoL15r) from baseline and cycle baseline by cycle • Changes in EuroQoL 5 Dimensions 5-Level (EQ-5D-5L) visual analog scale (VAS) score from baseline and cycle baseline over time by cycle • EQ-5D-5L responses to 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, anxiety/depression) over time by cycle
• To evaluate feasibility of self-administration of efgartigimod PH20 SC	• Number and percentage of participants who performed self-administration at home over time by cycle • Number and percentage of caregivers who administered the injection to the participant at home over time by cycle • Number of training visits needed for the participant or caregiver to be competent to start administering efgartigimod PH20 SC • Number and percentage of self- or caregiver-supported study drug administration among all study treatment visits at home
Exploratory	
• [redacted]	• [redacted] • [redacted]

4. STUDY DESIGN

4.1. Overall Design

- This is a phase 3, multicenter, long-term, single-arm, open-label study to evaluate the long-term safety and tolerability of efgartigimod PH20 SC 1000 mg. The clinical efficacy, PD, PK, immunogenicity, impact on the QoL of the participants, treatment satisfaction, mode of administration participant preference, and the feasibility of self-administration and caregiver-supported administration will also be assessed.
- The total study duration is from the participant's first visit in this study until, at the latest, 31 Dec 2024 (See Section 1.1):
  - Year 1: 3-week TPs of once weekly injections, repeated as needed with at least 28 days between TPs
  - Year 2 onward: 3-week TPs of once weekly injections. It is recommended to have IPs of at least 28 days, but a subsequent treatment period can be administered earlier based on clinical evaluation at the discretion of the investigator. A minimal interval of 7 days after the last IMP administration of the previous cycle must be maintained.
- The primary target population is adult patients with gMG who have previously participated in studies ARGX-113-2001 or ARGX-113-1705.
  - Study ARGX-113-2001 is a phase 3, randomized, open-label, parallel-group study comparing the PD, PK, efficacy, safety, tolerability, and immunogenicity of efgartigimod PH20 SC and efgartigimod IV in patients with gMG. Participants either receive efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg q7d for a total of 4 doses, after which there is a follow-up period of approximately 50 days.
  - Study ARGX-113-1705 is a phase 3, single-arm, open-label, multicenter extension study evaluating the long-term safety and tolerability of efgartigimod IV in patients with gMG. Participants receive efgartigimod IV 10 mg/kg q7d for a total of 4 infusions, followed by an intertreatment cycle of variable length dependent on the patient's clinical response to efgartigimod. Participants may continue this cycle for up to 3 years, receiving efgartigimod IV based on their clinical need.
- Participants must be receiving concomitant medication for gMG to enter the study and they must be on a stable dose of concomitant medication to be eligible for retreatment. Participants who have recently altered their concomitant medication dosage will start the study with an IP. See Section 6.8.2.
- At study entry, participants will be evaluated for the need of retreatment. Refer to the SoA in Section 1.3 for timing of retreatment.
- Efgartigimod PH20 SC will be administered by injection into the abdominal subcutaneous tissue or into the subcutaneous tissue of another appropriate injection site. Participants or their caregivers will be trained in IMP administration. A caregiver

is a person of legal age from the participant's social network (eg, family, relatives, friends) introduced by the participant. After signing an informed consent form (ICF) and receiving the necessary training, the caregiver can administer the SC injections to the participant. If the participant or caregiver completes the training to the satisfaction of the investigator, the participant or caregiver will be permitted to administer the investigational medicinal product (IMP).

- Participants and their caregivers must complete the training to the satisfaction of the site staff (a minimum of 1 site visit) before (self-)administering efgartigimod PH20 SC under the supervision of the site staff. Participants and caregivers who were in the SC arm in antecedent study ARGX-113-2001 and considered competent to (self-)administer may (self-)administer efgartigimod PH20 SC at home as of the second visit of the first TP. Participants and caregivers from the IV antecedent studies who are considered competent to (self-)administer may do so at home as of the second visit of the second TP onward. All participants must come to the site for the first administration of a TP, even if the participant or caregiver administers.

4.2. Scientific Rationale for Study Design

The aim is to evaluate the long-term safety and tolerability of efgartigimod PH20 SC 1000 mg and its efficacy in patients with gMG. Efgartigimod PH20 SC 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 depolymerizes hyaluronan under physiologic conditions and acts as a permeation enhancer, allowing for a larger volume to be injected with limited swelling or pain.[4]

As per the primary objective (Section 3), long-term safety and tolerability will be assessed by measuring the incidence and severity of TEAEs, including SAEs, AESIs, electrocardiogram (ECG) results, and clinical laboratory assessments over time. These metrics provide a broad view of potential safety concerns and allow a more detailed safety profile for efgartigimod PH20 SC.

An open-label, single-arm design allows for accrual of long-term safety data over multiple TPs to verify the overall safety and tolerability profile of the SC formulation of efgartigimod.

IgG autoantibodies lead to gMG symptoms, resulting from destruction of important molecules in the NMJ, including AChR. Total IgG levels and levels of AChR-Abs will be evaluated in the first year of the study as objective surrogate measures for the treatment efficacy of efgartigimod in gMG. Clinical efficacy will be measured by the MG-ADL total score, which is a well-established measure for assessing disease severity. Furthermore, study ARGX-113-1704 showed that reductions in the MG-ADL total score were consistent with reductions in levels of total IgG and AChR-Abs and followed a similar time course. Any effect on the QoL of the participants will be measured using the MG-QoL15r and EQ-5D-5L assessments, which are standardized assessments for quality of life related to gMG symptoms and generic health status, respectively.

[redacted]

4.3. Justification for Dose

The efgartigimod PH20 SC dose selected targets a similar total IgG reduction 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). In 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.

A proportion of participants have clinically significant worsening of symptoms at the end of the required minimum 28-day IP. Treatment management aims at minimizing fluctuations in disease severity. Therefore, some participants may benefit from earlier initiation of the subsequent cycle. Thus, earlier initiation of the next cycle will be allowed from the second year of treatment onward. This adaptation is not expected to raise any safety issues. Efgartigimod has been tested in once weekly and biweekly treatment regimens in other indications such as ITP and PV, and no safety concerns were identified with this treatment regimen, compared to the safety profile in cyclic dosing. Refer to the current IB for more details.

4.4. End of Study Definition

The end of the study is defined as the date of the last participant's last visit.

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 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
2. Previously participated in antecedent studies ARGX-113-2001 or ARGX-113-1705 and are eligible for rollover as defined by:
   a. For ARGX-113-2001
      – Completed the study and performed the EoS visit, or
      – Were discontinued from study treatment for reasons other than pregnancy or a life-threatening SAE. Receiving rescue therapy is not exclusionary unless given in a response to a life-threatening situation
   b. For ARGX-113-1705
      – Performed the end of part A, or
      – Started Part B, received the previous dose of efgartigimod IV at least 30 days prior to entry into this study, completed at least 1 year of study ARGX-113-1705, and performed the early discontinuation visit in ARGX-113-1705
      – Did not have 3 consecutive treatment failures in ARGX-113-1705 Part A, even if the participant received rescue therapy (unless rescue therapy was given in response to a life-threatening situation). Treatment failure is defined as the absence of a decrease of at least 2 points in total MG-ADL score compared to the subsequent TP baseline in at least 50% of the assessments
      – Are still receiving concomitant gMG medication. Participants who have stopped taking any concomitant medication for gMG are not eligible for rollover
      – Participants may rollover from ARGX-113-1705 until recruitment for this study is closed
3. Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies and:
   a. Male participants
      – Refer to Section 10.5.2.2.
   b. Female participants
      – WOCBP (defined in Section 10.5.1) must have a negative urine pregnancy test at baseline before IMP can be administered.

- The contraceptive requirements for WOCBP are described in Section 10.5.2.

5.2. Exclusion Criteria

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

1. The participant was discontinued early from studies ARGX-113-2001 or ARGX-113-1705, unless the reason for discontinuation from study ARGX-113-1705 was to rollover into study ARGX-113-2002
   a. Participants who, in the investigator's judgment, are not benefiting from efgartigimod IV in study ARGX-113-1705 Part B are not eligible for rollover into ARGX-113-2002
2. Are pregnant or lactating, or intend to become pregnant during the study or within 90 days after the last dose of IMP
3. Have any of the following medical conditions:
   a. Clinically significant uncontrolled chronic bacterial, viral, or fungal infection at rollover
   b. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with 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 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
4. Received a live-attenuated vaccine within 28 days prior to study entry or plan to receive a live-attenuated vaccine during the study
5. Had a known hypersensitivity reaction to efgartigimod, rHuPH20, or any of its excipients

5.3. Lifestyle Considerations

Participants will need to be fasted for each on-site visit at which safety laboratory assessments will be performed. Fasted is defined as no food or drink for at least 8 hours prior to the visit. Permitted medications that the participant normally takes can be taken as usual before a visit.

5.4. Screen Failures

Eligibility to rollover must be verified at the last visit of the antecedent studies ARGX-113-2001 or ARGX-113-1705, which acts as the first visit of this study.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 SAE.

Results from assessments in the antecedent studies should be used to determine eligibility. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

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 a dose cannot be administered within a visit window as specified in the SoA (Section 1.3), then that dose will be skipped. See Section 7.1.1.

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

Table 5: Study Intervention Administered

Treatment Group	**Efgartigimod PH20 SC**
Intervention name	Efgartigimod solution for SC injection [redacted] mg/mL coformulated with rHuPH20
Type	Biologic
Dose formulation	Efgartigimod drug product of [redacted] mg/mL for a fixed dose of 1000 mg for SC injection coformulated with [redacted] U/mL rHuPH20
Unit dose strength(s)	[redacted] mg/mL
Dosage level(s)	1000 mg q7d for a total of 4 injections in a TP, with multiple TPs possible depending on clinical effect
Route of administration	SC injection
Use	Investigational
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and labeling	The IMP will be provided in glass vials and will be packed and labeled in secondary boxes. Each glass vial and box will be labeled as per country requirement.

6.2. Preparation/Handling/Storage/Accountability

For detailed instructions for preparation, handling, storage, and accountability, please refer to the pharmacy manual and applicable guidance materials for home administrations. Each participant or caregiver will receive a specific training for IMP administration and a manual on preparation, handling, storage and administration of the IMP.

6.2.1. Preparation

Efgartigimod for SC administration will be provided as a sterile, clear to opalescent, 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 IMP.

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 by an adequately trained participant or caregiver.

Home administration by the participant or caregiver is permitted once they are considered competent to do (refer to Section 4.1).

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. The investigator will be provided with the European Union qualified person release documents.

All study intervention 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 until the study intervention is received by the participant.

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 and when the participant is storing the IMP at home.

The investigator (or designee) is responsible for the correct and safe storage of the IMP assigned to the clinical site before the IMP is given to the participant for home administration. While at the clinical site, the IMP must be stored in a locked, secure storage facility maintained within the appropriate temperature ranges, with access limited to those individuals authorized to dispense the IMP.

Once the participants have the IMP outside of the clinical site, they are responsible for the correct storage of the IMP. The investigator (or his/her designee) must directly ask the participant if the IMP has been stored correctly. Participants will be instructed to contact the site if they think there is a problem with the storage conditions at home.

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).

When the IMP is being used in home administration, the investigator or his/her designee must directly ask the participant to ensure that the IMP is only being taken by the participant and that it is being properly stored at home. All IMP vials must be returned to the site for accountability, regardless of whether they were used.

6.3. Measures to Minimize Bias: Randomization and Blinding

As this is an open-label, single-arm study, no randomization or blinding will be performed.

6.4. Study Intervention Compliance

Participants and/or their caregivers will receive specific training for IMP administration of efgartigimod PH20 SC and guidance materials on preparation, handling, storage, and administration of the IMP (refer to Section 4.1).

When the study intervention is administered at home by the participant or caregiver, compliance with study intervention will be assessed at each visit, including phone visits. Compliance will be assessed by direct questioning during the visits and documented in the source documents and the electronic case report form (eCRF). Deviation(s) from the prescribed dosage regiment should be recorded.

A record of the quantity of efgartigimod PH20 SC dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop times and dates, including dates for intervention delays will also be recorded by the site staff when administration is performed at the site and by the participant when administration is performed at home. At every on-site visit, the study staff must review the administration log and patient diary with the participant.

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. Site staff will contact the participants for the scheduled phone visits and ensure that the participant is compliant with the IMP administration schedule. All dates, start and end times of IMP administration, and any deviations from the intended regimen must be recorded in the administration log and the eCRF.

Participants will be provided with an administration log, where they will record when the IMP was administered at home and if there were any issues with the IMP administration. Participants will also receive a patient diary to record any AEs (including injection site reactions) that have occurred, what concomitant medication they have been taking, any hospitalizations, emergency room (ER) admissions, and intensive care unit (ICU) admissions. Completed diaries have to be provided to the site staff whenever the participant visits the site. Data collected from the diaries will need to be entered into the eCRF by the site staff.

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. The designated CRO monitor will also review records if the IMP administration is performed at home.

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. If it is determined that a participant or their caregiver committed an error in administration, then the

participant or the caregiver will need to complete the administration training again. The site staff will then determine if the participant and caregiver are competent to continue administration without supervision. 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 the IMP in the scheduled dosing window. If a participant cannot receive the dose within the scheduled dosing window, that dose must be skipped. Participants who miss doses will be allowed to continue in the study. Dosing should resume in the next scheduled dosing window, unless there are medical concerns that indicate IMP administration would put the participant at undue risk.

6.4.2. Protocol Deviations

The investigator should not implement any deviation from or changes to the approved protocol, except when 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.

6.5.1. Retreatment Criteria

A participant may be retreated if the investigator determines that the participant's condition has deteriorated due to gMG symptoms and if the participant agrees to be retreated.

The investigator may start a new TP during an on-site IP visit. In this instance, the IP visit becomes the first visit of the new TP (TP_nV1). No activities will be duplicated. If a participant thinks they may need retreatment between on-site visits, they may contact the investigator to discuss retreatment and schedule the first visit of the new TP (TP_nV1).

The participant must meet all of the following criteria to be eligible for retreatment:

- The participant completed the previous TP
- The participant could benefit from retreatment according to the investigator's judgment
- There is no clinical or laboratory evidence of any concomitant disease that could confound the results of the study or put the participant at undue risk (eg, infection)
- At least 28 days has elapsed since the participant received any kind of rescue therapy
- For year 1:
  - At least 28 days has elapsed between treatment periods (ie, between the last dose of the previous TP and the first dose of the next TP)
- For year 2 onward:

  - At least 7 days has elapsed between treatment periods (ie, between the last dose of the previous TP and the first dose of the next TP). It is recommended to have intertreatment periods (IPs) of at least 28 days, but a subsequent treatment period can be administered earlier based on clinical evaluation at the discretion of the investigator.
- There must be at least 4 weeks left in the study for the participant, so that a full TP and the EoS visit can be performed.

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

At the end of the study, argenx cannot guarantee continued access for participants but will comply with all local laws and regulations.

6.7. Treatment of Overdose

For this study, a variation of less than 10% of the amount of efgartigimod PH20 SC that should be injected for each administration will not be considered an overdose or medication error. A variation of greater than 10% of the intended amount of efgartigimod PH20 SC will be considered a medication error and an overdose, if applicable, regardless of whether any AEs occur.

An overdose is defined as a deliberate or accidental administration of IMP to a participant at a dose more than 10% that was assigned to that participant per the study protocol.

A medication error is any preventable incident that may cause or lead to inappropriate IMP use or participant harm while the IMP is in the care of the health care professionals. Such an incident may be due to health care professional practice, product labeling, packaging and preparation, administration procedures, and/or systems, including prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and/or use.

In case of a suspected overdose and/or medication error, the participant must be treated according to standard medical practice based on the investigator's judgment. The suspected overdose and/or medication error must be documented, with the quantity of the excess dose, as well as any observed AEs that are associated with the overdose.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, or herbal supplements) that the participant is receiving at the time of enrollment 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

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 ongoing medication and procedures received by the participant must be recorded in the eCRF, including the start dates. Any information on prior medication from the antecedent studies ARGX-113-2001, ARGX-113-1704, and ARGX-113-1705 may be used in the analysis. For participants rolling over from ARGX-113-1705, all available vaccination history should be recorded. Any vaccination information that the participant or their caregiver can remember should be recorded in the eCRF, with the brand name of the vaccine and date of vaccination, if possible. When a vaccine requires multiple injections (eg, influenza vaccine, tetanus vaccination, and booster), only the most recent vaccination must be recorded.

6.8.2. Permitted Concomitant Medication and Procedures

At study entry, participants are required to be on concomitant therapy for gMG, as they were in the antecedent studies. Permitted concomitant therapy for gMG includes:

- Nonsteroidal immunosuppressant (NSIDs) (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide)
- Steroids
- Acetylcholinesterase (AChE) inhibitors

To be retreated at study entry, participants must be on a stable dose of concomitant therapy for gMG. Therefore, participants entering this study from ARGX-113-1705 that have recently adjusted their concomitant medication will have to wait to be retreated in this study for the following time periods after changing their concomitant medication:

- NSIDS: 3 months
- steroids: 1 month
- AChE inhibitors: 2 weeks

In the first year, participants will be allowed to reduce the dose of a corticosteroid, an NSID, or an AChE inhibitor during IPs, but only after the first IP visit following a TP.

During the second year of the study, there will be no restrictions on changes to any concomitant gMG treatment.

All changes in concomitant gMG treatment and the reason for the change must be recorded in the eCRF.

Throughout the entire study, participants may be treated with plasma exchange (PLEX), Ig therapy or immunoadsorption (as a combination or monotherapy) as rescue therapy a maximum of 3 times per year if it is not for a life-threatening condition (see Section 6.8.3).

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 during the study should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration (see Section 8.2.9).

Standard therapies for concurrent medical conditions are permitted if they are not listed as prohibited in Section 6.8.3.

6.8.3. Prohibited Medications and Procedures

If any of the following prohibited therapies are used, participants must be discontinued from the study:

- any monoclonal antibody
- other experimental/study IMP
- live or live-attenuated vaccines

In the first year of the study, participants are also not allowed to do any of the below activities. However, participants will not be discontinued from the study in case of a protocol deviation due to the following prohibited activities:

- increase the dose or frequency of corticosteroids
- start a new type of steroids
- increase the dose or frequency of an NSID
- start a new NSID
- increase the dose or frequency of an AChE inhibitor
- decrease the dose or frequency of a corticosteroid, an NSID, or an AChE inhibitor from TP_nV1 through IP_nV1

6.8.4. Rescue Therapy

PLEX, Ig therapy, immunoadsorption, an increased dose of the current corticosteroid, or the use of a different corticosteroid used as a monotherapy or in combination with another therapy 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 item on the MG-ADL scale compared to the previous visit

The date and time of rescue medication administration, and the name, dosage regimen, and response to the rescue medication will be recorded in the eCRF. Prior to administration of rescue therapy, the MG-ADL total score should be recorded if possible.

Participants who receive rescue therapy under the previously listed conditions will not be discontinued from the study unless rescue therapy is given in response to a life-threatening

situation. Participants may not receive PLEX, Ig therapy, or immunoadsorption more than 3 times per year. When rescue therapy is needed, what therapy was used and the response to that therapy must be documented in the eCRF. The MG-ADL total score will be used to measure the response to the therapy at the safety follow-up (SFU) visit.

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. IMP Discontinuation

It may be necessary for a participant to permanently discontinue IMP. If IMP is permanently discontinued, the participant will not remain in the study (see Section 7.2).

7.1.1. Temporary Discontinuation of Study Intervention

Temporary discontinuation of study intervention is defined as an interruption of only the current TP. Participants may have a temporary discontinuation of the study intervention without being required to discontinue early from the study. Participants could have a temporary discontinuation from the study due to a temporary medical condition that puts the participant at undue risk (ie, symptoms of infection). These participants may still be eligible for additional doses of efgartigimod PH20 SC. If a dose cannot be administered within a visit window as specified in the SoA (Section 1.3), then that dose will be missed (Section 6.4.1), and the treatment discontinuation and reason for the missed doses will be documented. The next planned IMP dose can be administered to the participant at the next scheduled TP visit if the investigator determines that the undue risk has been resolved. The participant must continue to participate in all remaining TP visits, regardless of whether the IMP will be administered. During the first year of the study, if the last dose(s) of a TP are missed, a new TP can start only after at least 28 days have elapsed since the last dose of efgartigimod PH20 SC was administered. During the second year of the study onward, if the last dose(s) of a TP are missed, a new TP can start only after at least 7 days have elapsed since the last dose of efgartigimod PH20 SC was administered. Participants can remain in the study regardless of how many doses are missed.

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 or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

See Section 1.3 for data to be collected at the time of study discontinuation and follow-up and for any evaluations that need to be completed.

Participants who discontinue early from the study at a study visit should perform the activities for the end of treatment (ET) visit if 49 days (±2 days) has not elapsed since the last dose of efgartigimod PH20 SC. These participants will not receive any further administration of efgartigimod PH20 SC during the study and will return for the SFU visit at least 49 ±2 days after the last dose administration. If 49 ±2 days has already elapsed since the last dose of efgartigimod PH20 SC, then this visit becomes the SFU visit and the SFU visit activities must be performed.

Participants who discontinue early from the study between visits should perform the SFU visit at least 49 ±2 days after the last dose of efgartigimod PH20 SC. If 49 ±2 days has already elapsed, then the SFU visit will be planned as soon as possible.

The participant will be permanently discontinued from both the study intervention and from the study at that time.

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 in the study records and inform the sponsor as soon as possible.

Participants **must** be discontinued from the study and complete the ET visit (if applicable) and the SFU visit at least 49 ±2 days after the last administered dose and as specified in the SoA, (Section 1.3) if:

- the investigator determines 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)
- the participant receives rescue therapy in response to a life-threatening situation (Section 6.8.4)
- the participant receives rescue therapy more than 3 times per year
- 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)
- participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship

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 information 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 10.1.9.

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.

At study entry, 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.

The investigator must confirm that potential participants meet all eligibility criteria. The investigator will record details of all participants to confirm eligibility.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3). Clinical efficacy will be measured using the MG-ADL scale and quality of life will be measured using the MG-QoL15r and EQ-5D-5L.[5,6]

8.1.1. 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. If possible, the same evaluator should administer the MG-ADL for a given participant throughout the study. It is recommended to perform the MG-ADL scale prior to all other assessments.

8.1.2. MG-QoL15r

The 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.

8.1.3. EQ-5D-5L

The 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 the (or placing a cross 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 VAS is included in the questionnaire. Participants 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."

8.1.4. Pharmacodynamics

Total IgG levels and AChR antibody levels (in AChR-Ab seropositive participants only) will be measured using validated methods from blood samples as indicated in Section 1.3. The actual

date and time of the blood sample collection will be collected and included in the central laboratory data transfer.

8.2. Safety Assessments

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

8.2.1. Demography

Demography information will be copied over from antecedent studies ARGX-113-2001 and ARGX-113-1705.

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. 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 include temperature, systolic and diastolic blood pressure, and pulse.

It is recommended that the method used to measure body temperature at study entry is maintained throughout the study.

Blood pressure and pulse measurements will be assessed in a semi-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 ECGs will be obtained predose on dosing days, using an ECG machine.

8.2.5. Medical and Surgical History

Medical history from the antecedent studies ARGX-113-2001, ARGX-113-1704, and ARGX-113-1705 will be used.

8.2.6. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed. 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 will be collected 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 and an SAE, then it must be recorded on the SAE form.

8.2.6.1. Hematology, Clinical Chemistry, Coagulation Panel and Urinalysis

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. SARS-CoV-2 Test

Nasal and throat mucosal cell samples will be collected according to the laboratory manual at the time points to be tested for SARS-CoV-2 as needed. Participants should only be tested if they have symptoms of COVID-19 or if they were in contact with someone who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements. See Section 10.6.

8.2.7. Pregnancy Testing

Urine tests for pregnancy will occur for WOCBP at the time points specified in the SoA (Section 1.3). Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFU).

Additional pregnancy testing could be performed as necessary by the investigator or as required by local regulations, to establish the absence of pregnancy at any time during the study.

8.2.8. Immunogenicity

8.2.8.1. 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. The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual.

As per regulations, all samples will be analyzed in a 3-tiered approach using validated methods:[7]

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 NAb assay to assess the ADA for neutralizing activity.

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

8.2.8.2. 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), including a sample taken at the first visit of the first TP (TP_1V1) for participants coming from study ARGX-113-1705 and for participants coming from study ARGX-113-2001 who received efgartigimod IV. Sampling will be done predose on IMP administration visits. The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual. If no sample was taken, the reason will be recorded.

As per regulations, samples will be analyzed in a 3-tiered approach using validated methods:[7]

1. 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.

Samples taken during the second year will only be analyzed if needed for safety purposes.

8.2.9. Vaccine Antibody Titers and PBMCs

Additional blood samples (serum/peripheral blood mononuclear cells [PBMCs]) may need to be taken for additional/optional/future/vaccination research if the participant consents. If a participant consents to this additional sampling, the following samples are to be taken in case of vaccination:

- The baseline serum sample can be taken at any moment before the vaccination is administered. This sample does not have to be taken at the baseline visit.
- The second serum sample is to be taken at least 4 weeks after the vaccine has been administered.
- A third serum sample is to be taken at the first IP_nV1 that is at least 4 weeks after the vaccine has been given. In case the visits of the second and the third sample coincide, then only 1 sample is needed.

Serum samples only need to be taken when a vaccination is planned (baseline sample) or after a vaccination has occurred (second/third sample).

In addition, a whole-blood sample to isolate PBMCs will be collected at study entry and then approximately every 3 months throughout the study during a scheduled on-site visit, regardless of the vaccines a participant has received. The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual.

8.2.10. Suicidal Ideation and Behavior Risk Monitoring

Efgartigimod PH20 SC is being developed for a neurologic indication. Therefore, per US Food and Drug Administration (FDA) guidance, suicidal ideation and behavior (SIB) risk monitoring is required.[8]

Participants being treated with efgartigimod should be monitored appropriately and observed closely for SIB 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 SIB, should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of SIB and intervention emergent SIB will be monitored by asking the following question derived from the 9-item Patient Health Questionnaire (PHQ-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, Serious Adverse Events, 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, or surrogate).

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 10.4.3 and Section 10.4.4.

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 or the SFU visit at the time points specified in the SoA (Section 1.3). Ongoing AEs from the antecedent studies must also be recorded.

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 the information 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 AESIs 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 IRB/IEC 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 from when the participant enters the study 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 ICF 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 perform the ET visit (if applicable) and the SFU visit, as described in Section 7.2.

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

8.3.7. AEs of Clinical Interest

8.3.7.1. Injection-Related Reactions

All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. As with any SC injection, injection-related reactions can occur during or after administration.

Overall, the frequency of injection-related reactions in clinical studies has been low.

The efgartigimod IB provides more information on injection-related reactions.

8.3.7.2. Injection-Site Reaction

An injection-site reaction is any AE developing at the injection site. Localized injection-site reactions were observed in studies of efgartigimod with PH20 administered SC. The most frequently reported injection-site reaction AEs are *Injection site erythema*, *Injection site pain*, and *Injection site swelling*.

Any injection-site reaction will be reported as an AE (Section 8.3). Certain types of local reactions could be photographed and shared with the sponsor for review and assessment.

As a routine precaution, participants will be trained or observed closely by a trained health-care professional for any potential injection-site reaction.

Refer to the current IB for more information on injection-site reactions.

8.4. Pharmacokinetics

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

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.

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.

PK sampling will be done predose (within 1 hour prior to the injection) at study entry.

To characterize anticipated peak concentrations, efgartigimod concentrations will also be measured in a subset of at least 12 participants who consent to additional sampling. These participants will perform additional on-site visits 2 days after their first and fourth injections in a treatment period. These additional visits can only be performed when all of the injections of that treatment period are given at the site. This sampling may only be performed during a participant's first and/or second treatment periods.

8.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.6. Biomarkers

See Section 8.1.4 for assessments of total IgG levels and AChR autoantibody levels.

8.7. Immunogenicity Assessments

See Section 8.2.8 for immunogenicity assessments.

8.8. Medical Resource Utilization and Health Economics

Medical resource and health economic parameters including ER visits, hospitalizations, and ICU admissions will be recorded in the eCRF to allow for the assessment of change in these parameters with efgartigimod PH20 SC treatment. Historical data on these parameters for at least 12 months prior to the start of the study will be collected only for participants rolling over from ARGX-113-1705.

8.8.1. [redacted]

[redacted]

8.8.2. [redacted]

[redacted]

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 biomarkers, and methods used for vaccination antibody testing and any other additional research interests.

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 an interim or 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

Not applicable to this one-arm, open-label long-term safety study.

9.2. Sample Size Determination

No sample size calculation is needed in this study. Up to 201 participants may be enrolled from the antecedent studies ARGX-113-2001 and ARGX-113-1705.

Note: "Enrolled" means a participant's agreement to enter 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.

9.3. Analysis Sets

The analysis set defined in Table 6 will be used for all analyses.

Table 6: Analysis Sets

Analysis Sets	Description
Safety analysis set	All participants who are exposed to IMP in this study
Full analysis set	All participants who are exposed to IMP in this study

9.4. Statistical Analyses

The SAP will be finalized prior to an interim or final database lock and it 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

Since all participants will receive the same treatment in this open-label long-term safety study, analysis of all endpoints will be essentially descriptive. All endpoints will be summarized with descriptive statistics by treatment arm in study ARGX-113-2001 and overall among participants from study ARGX-113-2001 and also by AChR-Ab status and overall among all participants from both study ARGX-113-2001 and study ARGX-113-1705.

Summary statistics will be provided for the continuous endpoints (eg, MG-ADL total score, levels of total IgG and AChR-Abs, MG-QoL15r score, EQ-5D-5L VAS score, laboratory values, vital signs) over time (by cycle and over applicable study visits) in terms of absolute values, changes from study baseline and changes from cycle baseline.

Frequency tables will be generated for all categorical endpoints (ie, AEs, ADA against efgartigimod and ADA against rHuPH20, and EQ-5D-5L responses to 5 dimensions by cycle and overall).

9.4.2. Primary Endpoint(s)

Summary statistics will be provided for the continuous endpoints and frequency tables will be generated for all categorical endpoints.

9.4.3. Secondary Endpoint(s)

Summary statistics will be provided for the continuous endpoints and frequency tables will be generated for all categorical endpoints.

9.4.4. Exploratory Endpoints

[redacted]

9.5. Interim Analysis

Interim analyses might be performed to support questions for 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 serious adverse events (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. Investigators 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

Before 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 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 procedures to 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 enters the study.

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.

A separate ICF will be issued to all caregivers. Caregivers must sign the ICF before being trained in IMP administration. A copy of the signed and dated caregiver ICF(s) must be provided to the caregiver.

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.

A copy of the signed and dated ICF(s) must be provided to the participant.

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 contract research organization (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 in the eCRF 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 eCRF.

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 CRF 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 (CSR)
- 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. The investigator/institution should maintain a record of the location(s) of their respective essential documents, including source documents.

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.

The definition of what constitutes source data can be found in the investigator source data agreement.

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 CRF 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
- An unexpected negative change to the benefit-risk profile of the IMP
- Recommendation of termination by the DSMB
- A necessary adjustment to the maximum insured sum for the study that is not possible
- Regulatory agency and/or IRB/IEC approvals withdrawn

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 contract research organization(s) 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 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 7 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 7: Protocol-Required Safety Laboratory Tests

Laboratory Test	Parameter			
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV % reticulocytes	WBC count with differential[a]: basophils eosinophils lymphocytes monocytes neutrophils	
Clinical chemistry	BUN	potassium	AST/SGOT	albumin
	creatinine	sodium	ALT/SGPT	CRP
	glucose	calcium	ALP[b]	Bilirubin, total and direct
	HbA1c	GGT	HDL	LDL (measured)
	LDH	triglycerides	total cholesterol	creatinine clearance
Coagulation panel	aPTT	PT	INR	
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	Urine hCG pregnancy test[c] (as needed for women of childbearing potential, defined in Section 10.5)			
Unscheduled tests	SARS-CoV-2			

ALP=alkaline phosphatase; ALT/SGPT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST/SGOT=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=γ Glutamyl transferase; HbA1c=glycosylated hemoglobin; hCG=human chorionic gonadotropin; HDL=high density lipoprotein; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low density lipoprotein; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; WBC=white blood cell

Note: All samples for safety laboratory tests will be taken with the participant in the fasted state (8 hours).

[a] These will be measured in percentage and absolute numbers.

[b] Consider fractioning for elevated alkaline phosphatase levels.

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

The maximum amount of blood collected from each participant is 1493.4 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 AE and/or SAE

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 to 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, and 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 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 Reporting Mailbox/Fax on page 2.

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered to be of childbearing potential unless she is either:

- postmenopausal: A postmenopausal state is defined by continuous amenorrhea for at least 1 year without an alternative medical cause with a follicle-stimulating hormone (FSH) measurement of >40 IU/L. A historical FSH measurement of >40 IU/L is accepted as proof of a postmenopausal state for women on hormone replacement therapy.
- Surgically sterilized: Women who have had a documented permanent sterilization procedure (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

10.5.2. Contraception Guidance

10.5.2.1. Female Contraception for Women of Childbearing Potential

WOCBP must use a highly effective or acceptable contraception method, which should be maintained at minimum until 90 days after the last dose of IMP.

Highly effective methods of contraception are:

1. Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    a. Oral
    b. Intravaginal
    c. Transdermal
2. Progestogen-only hormonal contraception associated with the inhibition of ovulation
    a. Oral
    b. Injectable
    c. Implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence
    - 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.

Acceptable methods of contraception are:

1. Progestogen-only hormonal contraception in which inhibition of ovulation is not the primary mode of action
    a. Oral
    b. Injectable
    c. Implantable
2. Male or female condom with or without spermicide
3. Cap, diaphragm, or sponge with spermicide

10.5.2.2. Male Contraception

No male contraception is required.

10.6. Appendix 6: Possible Adaptations to Study Protocol During COVID-19 Pandemic

During the 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 and the site staff, while still evaluating the long-term safety and tolerability of efgartigimod PH20 SC. 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.

10.6.1. 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 IV formulation of efgartigimod has been administered to over 250 participants, including healthy volunteers and patients with generalized myasthenia gravis (gMG), immune thrombocytopenia, and pemphigus, with no infection-related safety concerns identified. The efgartigimod PH20 SC doses used in study ARGX-113-2002 have been administered to healthy volunteers and patients with chronic inflammatory demyelinating polyneuropathy, 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.

10.6.2. COVID-19 Risk Mitigation

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.

All participants with clinically significant uncontrolled infections, malignancies, or recent surgeries are excluded (see Section 5.2). If at any point a participant tests positive for SARS-CoV-2, the administration of efgartigimod PH20 SC will be temporarily discontinued until the participant's symptoms have resolved and they no longer test positive for SARS-CoV-2. 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.

Home administration by a participant or caregiver is permitted for many of the TP visits in the study and IP visits are permitted to alternate between on-site visits and phone visits. Thus, the

number of necessary on-site visits is minimal, reducing the risk to participants and site staff of contracting COVID-19.

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

10.6.3.1. 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 the sponsor/CRO and can be extended based on local epidemic status.

10.6.3.2. Testing for COVID-19

Testing for COVID-19 beyond what is mandated by relevant local authorities is not required during the study. However, it is recommended that participants who develop COVID-19 symptoms during the study or have contact with someone who tested positive for SARS-CoV-2 be tested.

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.

At study entry, if the participant cannot come to the site due to COVID-19 infection or travel restrictions, the ICF can be signed remotely. If a participant is infected with COVID-19, they cannot be (re)treated until they no longer test positive for SARS-CoV-2 and no longer have symptoms of a COVID-19 infection. These participants can still enter the ARGX-113-2002 study by entering an IP.

10.6.3.3. Study Protocol Changes

If the COVID-19 pandemic results in participants being unable to visit the site, a home nurse can perform visits that are mandatory to be performed at the site (Section 1.3). A home nurse will be a qualified person from either the study site staff or a home health care vendor if allowed per local requirement. The use of a home nurse will depend on regional availability. If a home nurse is being used, the visits can take place at the participant's home or an alternative location agreed upon by both parties. Additionally, all IP and TP visits, except TP_nV1 and the first 2 visits of the IP that occur before the first TP (IP0), can be performed by phone if necessary. In the first year, the first visit of an IP after a TP, called IP_nV1, must occur on-site. The second IP visit (IP_nV2) will also be on-site. Subsequent visits may alternate between telephone and on-site visits. During an IP, consecutive telephone visits are not allowed, except in exceptional circumstances caused by the COVID-19 pandemic and after approval by the sponsor and/or the CRO.

The COVID-19 pandemic may lead to restrictions that reduce the ability of study monitors to travel to the sites to verify source data, protection of participant safety and rights, and compliance to the protocol, other study agreements, ICH GCP guidelines, and applicable regulatory requirements. In these cases, remote monitoring will be performed where possible and permitted by local regulations. Any remote access will exclusively use a secure electronic system that is compliant with local regulations. Participants will be informed of this possibility before giving consent.

10.6.3.4. 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, injection site reactions, suicide ideation and behavior monitoring, IMP administration, who performed the administration, training and competency to perform self-administration, MG-ADL total score, quality of life assessments (first year only), [redacted]

10.7. Appendix 7: Abbreviations and Definitions

10.7.1. Definitions

Baseline: the data collected prior to the first dose of efgartigimod in this study

Caregiver: a person of legal age from the participant's social network (eg, family, relatives, friends) introduced by the participant. After receiving the necessary training, the caregiver can administer the SC injections to the participant

Cycle: a period that includes both a TP and the corresponding IP and ends immediately prior to the first dose of the next TP

Cycle baseline: the data collected prior to the start of each cycle

Enrolled: A participant's agreement to enter 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.

10.7.2. Abbreviations

AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	anti-acetylcholine receptor antibody
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EoS	end of study
ER	emergency room
ET	end of treatment
FcRn	neonatal Fc receptor
FSH	follicle-stimulating hormone

gMG	generalized myasthenia gravis
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	investigational new drug
IP	intertreatment period
IP_nVm	intertreatment period (period number) visit (visit number)
IRB	Institutional Review Board
IV	intravenous(ly)
[redacted]	[redacted]
MG-ADL	Myasthenia Gravis Activities of Daily Living
MG-QoL15r	Myasthenia Gravis Quality of Life 15 item scale revised
NAb	neutralizing antibody
NMJ	neuromuscular junction
NSID	nonsteroidal immunosuppressant
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PH20	recombinant human hyaluronidase PH20 (rHuPH20)
PHQ-9	9-item Patient Health Questionnaire
PK	pharmacokinetics
PLEX	plasma exchange
PPE	personal protective equipment
PT	prothrombin time
q2w	every 2 weeks (biweekly)

q7d	every 7 days
QMG	Quantitative Myasthenia Gravis
QoL	quality of life
QRS	duration of ventricular depolarization
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SC	subcutaneous(ly)
SFU	safety follow-up
SIB	suicidal ideation and behavior
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse events
[redacted]	[redacted]
TP	treatment period
TP_nVm	treatment period (number) visit (number)
UNS	unscheduled
VAS	visual analog scale
WOCBP	woman of childbearing potential

10.8. Appendix 8: Germany-Specific Requirements

10.8.1. Overview

To align with the upcoming Regulation (EU) No. 536/2014, this protocol amendment supersedes prior country-specific amendments. Therefore, all changes from the Germany-specific v2.2 protocol were incorporated with the below exceptions that were first implemented in the Germany-specific v1.5 protocol. The following changes were not included in the global protocol v3.0 because they were only applicable to the starting phase of the study:

- An obligatory treatment-free visit at the start of the study to test for SARS-CoV-2 before IMP
- Exclusion criterion for being infected with SARS-CoV-2
- Exclusion criteria to comply with Section 7 (3), No. 4 GCP Regulation and Section 40 Para. 1 S.3 No.4 AMG (German Drug Law), respectively

10.8.2. Germany-Specific Document History

Germany-Specific DOCUMENT HISTORY	
Document	**Date**
Protocol version 1.1-Germany	19 May 2021
Protocol version 1.2-Germany	02 Jun 2021
Protocol version 1.3-Germany	10 Jun 2021
Protocol version 1.4-Germany	07 Jul 2021
Protocol version 1.5-Germany	02 Aug 2021
Protocol version 2.1-Germany	22 Sep 2021
Protocol version 2.2-Germany	07 Jun 2022
Protocol version 3.0 (global, to supersede Germany v2.2)	02 Feb 2023

10.8.3. Summary of Changes Between Protocol Version 2.1-GER and Protocol Version 2.2-GER

Overall Rationale for the Changes in Protocol Version 2.2-Germany

The changes implemented in the protocol were include in 3 protocol clarification letters (dated 05 Oct 2021, 01 Dec 2021, and 01 Feb 2022) and have been updated into an amendment at the request of the competent authorities.

The major changes from protocol version 2.1 compared with protocol version 2.2 are summarized in the following table. A double strikethrough indicates text that was removed and bold text indicates text that was added. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized.

Section and Name	Description of Change	Brief Rationale
Protocol Signature Page	[redacted], MD, PhD is now the sponsor signatory for this protocol.	Effective 01 Apr 2022, Dr. [redacted] became the sponsor's chief medical officer.
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~~n~~ **therapeutic** intervention ~~or collection of data~~ until the completion of the study.	Clarified that participants enrolled in another study not involving a therapeutic intervention should not be excluded or discontinued

8.2.9.2 ADA Against rHuPH20 Other sections impacted by the added text: 1.3 Schedule of Activities, footnote r	Blood samples will be collected to assess the plasma levels of ADA against rHuPH20 … for participants coming from study ARGX-113-1705 **and for participants coming from study ARGX-113-2001 who received efgartigimod IV.**	Corrected the omission of ADA sampling for participants coming from study ARGX-113-2001 who received efgartigimod IV
8.2.10 Vaccine Antibody Titers and PBMCs Other sections impacted by the edited text: 1.3 Schedule of Activities, footnote q	If a participant ~~that~~ consents to this additional sampling ~~receives a vaccination during the study, a baseline serum sample prior to the vaccination will be taken and a serum sample will be taken at least 4 weeks after the vaccine was administered. The closest visit that is at least 4 weeks after the vaccine was administered may be used. If this visit does not coincide with IPnV1, then another sample will also be taken at this visit~~, **the following samples are to be taken in case of vaccination:** • **The baseline serum sample can be taken at any moment before the vaccination is administered. This sample does not have to be taken at the baseline visit.** • **The second serum sample is to be taken at least 4 weeks after the vaccine has been administered.** • **A third serum sample is to be taken at the first IPnV1 that is at least 4 weeks after the vaccine has been given. In case the visits of the second and the third sample coincide, then only one sample is needed.**	Clarified the time points when additional blood samples may be needed for additional/optional/future/ vaccination research if the participant receives a vaccination during the study
4.1 Overall Design Other sections impacted by the added text: 1.3 Schedule of Activities, footnote d	If a participant is not in need of retreatment, the next visit will be an IP visit. In this case, IP visits will be performed every 21 days and may alternate between on-site visits and phone visits. **However, the first 2 visits of an IP must be on-site, and 2**	Clarified that the first 2 visits of an IP, both before the first TP and after a TP, must be at the site

	consecutive phone visits are not allowed.	
8.2.9.2 ADA Against rHuPH20 Other sections impacted by the edited text: 1.3 Schedule of Activities, footnote r	Blood samples will be collected to assess the plasma levels of ADA against rHuPH20 as indicated in the SoA (Section 1.3), including a sample taken at ~~study entry~~ **the first visit of the first TP (TP_1V1) …**	Clarified that the baseline sample for ADA against rHuPH20 will not be obtained until the first visit of the first TP (TP_1V1)
4.1 Overall Design Other sections impacted by the added text: 1.3 Schedule of Activities, footnote w	~~Once participants or their caregivers are competent to perform IMP administration and they have performed at least 1 administration at the site under the supervision of the site staff, including during study ARGX-113-2001, participants will be allowed to administer efgartigimod PH20 SC at home or at the site. However, the first administration of a TP must always be done at the site.~~ **Participants and their caregivers must complete the training to the satisfaction of the site staff (a minimum of 1 visit) before (self-) administering efgartigimod PH20 SC under the supervision of the site staff. Therefore, a minimum of 2 visits is required for a participant or caregiver to be considered competent to administer efgartigimod PH20 SC at home. Participants and caregivers who were considered competent to (self-) administer and successfully (self-) administered at least once under supervision of the site staff in the antecedent study, ARGX-113-2001, may (self-) administer efgartigimod PH20 SC at home as of the second visit of the first TP. All participants must come to the site for the first administration of a TP, even if the participant or caregiver administers.** Subsequent administrations at visits 2, 3, and 4 of that TP can be performed at home.	Clarified that a minimum of 2 visits is required for a participant or caregiver to be considered competent to administer efgartigimod PH20 SC at home
10.2.1 Specialty Laboratory Tests	At the visits listed in the SoA (Section 1.3.), blood will be sampled under fasting conditions for specialty laboratory	Removed PCSK9 assessment from specialty laboratory tests

	parameters that may include but not be limited to apolipoprotein B (apoB), lipoprotein A, fibrinogen, von Willebrand factor, **and** d-dimer~~; proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9)~~.	
5.1 Inclusion Criteria	2a…Were discontinued from study treatment for reasons other than pregnancy or ~~an S(AE~~) **a life-threatening SAE.**	Clarified that a participant is eligible if they were discontinued due to an SAE that was not life-threatening
10.2 Appendix 2: Clinical Laboratory Tests, Table 3	Content in Table 3 of the Clinical Study Protocol ARGX-113-2002 v1.5-GER (02 Aug 2021) was restored.	Corrected the unintentional removal and insertion of laboratory parameters in Table 3 that occurred due to a reformatting issue in CTP v2.0 (10 May 2021)

10.8.4. Summary of Changes Between Protocol Version 1.5-GER and Protocol Version 2.1-GER

Overall Rationale for the Changes in Protocol Version 2.1-Germany

The overall rationale for this amendment includes adding additional optional pharmacokinetic samples from a subset of participants to better evaluate the pharmacokinetics of the investigational medicinal product (IMP), as requested by competent authorities. Additionally, more clinical chemistry laboratory assessments have been added to evaluate the effect of the IMP on lipid panels.

The major changes from Protocol Version 1.5 compared with Protocol Version 2.1 are summarized in the following table. A double strikethrough indicates text that was removed and bolded text indicates text that was added. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized.

Section and Name	Description of Change	Brief Rationale
Title Page	Industriepark **Zwijnaarde** 7 ~~B-~~9052 Zwijnaarde **(Ghent)** Belgium	Corrected argenx address
	Added name and affiliation of principal/coordinating investigator Added Investigator's Agreement and signature	Integrated investigator information into protocol
Emergency Contact Information	Added the Emergency Contact Information section with information about SAE reporting	Updated email address and fax number for reporting SAEs

Section 1.1 Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints	Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), **and AEs of special interest (AESIs)**, and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram results	Edited endpoints for clarity
	[redacted]	
	Added secondary objective and endpoint Objective: **To evaluate the PK of efgartigimod PH20 SC** Endpoint: **Efgartigimod serum concentrations**	Added an objective and endpoint to assess the PK with the additional optional PK assessments.
Section 1.1 Synopsis, Overall Design Section 4.1 Overall Design Section 10.8.1 Definitions	**A caregiver is a person of legal age from the participant's social network (eg, family, relatives, friends) introduced by the participant. After receiving the necessary training, the caregiver can administer the SC injections to the participant.**	Added the definition of the caregiver
Section 4.1 Overall Design	The total study duration is 2 years from the participant's first visit in this study: • 3-week treatment periods (TPs), repeated as needed based on the clinical effect, **with a maximum of 14 TPs**	Added information contained in the synopsis to the body of the protocol
Section 1.1 Synopsis Section 9.2 Sample Size Determination	"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.	Removed references to the participant's legally authorized or legally acceptable representative that are not applicable to this study.
Section 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	AEs will be reported by the participant (or, when appropriate, by a caregiver, **or** surrogate~~, or the participant's legally authorized representative~~).	
Section 1.3 Schedule of Activities	Added 2 visits, PK1 and PK2, to take place 2 days after the first and fourth dose in a treatment period, respectively. These visits have "Pharmacokinetics" activity row checked. Added footnote c **These are optional visits to collect additional PK samples from consenting participants. These additional visits can only be performed when all of the injections of that**	Added additional pharmacokinetic sampling visits to meet competent authority request for more PK sampling

	treatment cycle are given at the site. Sampling will only be performed during a participant's first and/or second treatment cycles.	
Section 8.4 Pharmacokinetics	**Efgartigimod concentrations will be measured in all participants at study entry and 1 week after the last injection of each treatment cycle.** ~~The following PK parameters will be measured: concentration observed predose (C_{trough}) of efgartigimod PH20 SC~~ **To characterize anticipated peak concentrations, efgartigimod concentrations will also be measured in a subset of at least 12 participants who consent to additional sampling. These participants will perform additional on-site visits 2 days after their first and fourth injections in a treatment cycle. These additional visits can only be performed when all of the injections in a treatment cycle are given at the site. This sampling may only be performed during a participant's first and/or second treatment cycles.**	
Section 1.3 Schedule of Activities	End of study visit study day changed ~~728~~730	Corrected the number of days to accurately reflect the study duration
	Footnote b This visit must always be performed at the site. **All other visits can be performed by phone if IMP administration occurs at home.**	Clarified which visits are phone visits
	Footnote y The first dose administration of all TPs…may be performed at home. **When IMP administration is performed at home, the associated visit will be performed by phone.**	
	Footnote u The PK assessments will only be taken at TP_1V1. The assessment should be performed predose. ~~only at TP_1V1.~~	Clarified the timing of the PK sampling
	Added row for "**Blood sampling**"	Rearranged the Schedule of Activities to group the blood sampling together
Section 1.1 Synopsis, Intervention Groups and Duration	Footnote c in Figure 1 Footnote d in Figure 2	Clarified study duration

Section 1.2 Schema Section 1.3 Schedule of Activities	Footnote f in Schedule of Activities The study will last for 2 years **from the participant's first visit in this study.**	
Section 1.3 Schedule of Activities Section 6.6 Continued Access to Study Intervention After the End of the Study	Footnote f in Schedule of Activities If efgartigimod becomes commercially available **for patients with gMG** or available through another patient program **for gMG**, participants will have the choice to switch to 1 of these options after 1 year of participation in this long-term safety study. **No treatment-free follow-up will be performed in this study, except for participants who do not want to continue receiving efgartigimod.**	Clarified procedures for continued access to IMP after the study
Section 1.3 Schedule of Activities Section 6.4 Study Intervention Compliance	Footnote x in Schedule of Activities Participants who have not previously self-administered…only be performed on-site. **At every on-site visit, the study staff must review the administration log and patient diary with the participant.**	Added the instruction to review the administration log and patient diary to check for compliance and adverse events
Section 1.3 Schedule of Activities	Footnote p Blood samples for clinical laboratory (hematology/clinical chemistry and FSH, if applicable) safety assessments will be collected. On dosing days, the samples will be taken predose. Participants need to be fasted (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.	Clarified policy on taking permitted medications before each sampling. Aligned fasted definition with previous studies
Section 1.3 Schedule of Activities Section 5.3 Lifestyle Considerations	Footnote p in the Schedule of Activities Participants will need to be fasted for each on-site visit **at which safety laboratory assessments will be performed**. Fasted is defined as no food or drink ~~except for water,~~ for at least 8 hours prior to the visit**. Permitted medications that the participant normally takes can be taken as usual before a visit.**	
Section 8.2.6.1 Hematology, Clinical Chemistry, and Urinalysis	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 for up to 4 hours prior to the assessment.~~	

Section 8.2.9.1 ADA Against Efgartigimod Section 8.2.9.2 ADA Against rHuPH20 Section 8.2.10 Vaccine Antibody Titers and PBMCs	**The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual.**	Added the location of the instructions for sampling
Section 1.3 Schedule of Activities Section 8.2.10 Vaccine Antibody Titers and PBMCs	Footnote r in the Schedule of Activities Additional blood samples (serum/peripheral blood mononuclear cells [PBMCs]) may need to be taken for additional/optional/future/**vaccination** research…occurred. In addition,~~if a participant consents to it,~~ a whole-blood sample to isolate PBMCs will be collected **at study entry and then** approximately every 3 months throughout the study during a scheduled on-site visit, regardless of the vaccines a participant has received.	Clarified that participants will have the option to consent to both serum and PBMC samples instead of one or the other. Added PBMC sampling at study entry
Section 1.3 Schedule of Activities	Footnote bb in the Schedule of Activities Adverse events, use of concomitant therapies, use of rescue therapy, medical procedures performed on participants, and hospitalizations will be collected informed consent signature until the last study-related activity. All available vaccination history for participants rolling over from ARGX-113-1705 ~~will be captured as a part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the study.~~**should be recorded in the eCRF. All vaccines received during the study should be recorded as concomitant medication.** See Section 6.8 and Section 8.3	Clarification on the recording of vaccination history and vaccines received during the study.
Section 8.2.6 Clinical Safety Laboratory Assessments	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 **and an** SAE, then **it** ~~the outcomes~~ must be recorded **on the SAE form.**	Simplified the text by removing redundant information
Section 8.2.6.1 Hematology, Clinical Chemistry	~~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 for 8 hours.~~ • ~~Blood samples for safety assessments will be collected according to the laboratory manual.~~ • ~~The samples will be analyzed at the central laboratory.~~	
Section 5.1 Inclusion Criteria	Criterion 3.a. Male participants: Male participants are not allowed to donate sperm from signing the ICF ~~through 90 days after the last dose of IMP~~ **until the end of the study.**	Updated contraceptive requirement to reflect new reproductive toxicity data
Section 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 will be provided** with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.	Edited the information regarding supplying the IMP for clarity
Section 6.4 Study Intervention Compliance	Errors that are identified…without supervision. ~~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.	Clarified administration error text.
Section 1.2 Schema, Figures 1 and 2 Section 6.5.1 Retreatment Criteria	Footnote a in the Schema **There must be at least 7 weeks left in the study for the participant, so that a full TP and IP can be performed.**	Added a retreatment condition to restrict starting treatment periods near the end of the study so that participants can complete a full treatment cycle
Section 6.7 Treatment of Overdose	~~A participant must not miss more than 2 consecutive doses and must not miss more than 10% of the total planned doses. Furthermore,~~ There must be at least 3 days between 2 consecutive doses.	Removed unnecessary restriction on missing doses

Section 6.8.1 Prior Medication and Procedures	For participants rolling over from ARGX-113-1705, all available vaccination history ~~must be collected~~ **should be recorded in the eCRF. Any vaccination information that the participant or their caregiver can remember should be recorded in the eCRF with the brand name of the vaccine and date of vaccination, if possible.**	Added vaccination history collection information for participants entering the study from study ARGX-113-1705
Section 6.8.2 Permitted Concomitant Medication and Procedures	Any vaccination ~~within 28 days of study entry up until the end of the study~~ **during the** study should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration.	Updated information on recording received vaccination so information can be used in a separate analysis
Section 6.8.3 Prohibited Medications and Procedures	In the first year of the study, participants are NOT allowed to do any of the following: … ~~change~~ **increase** the dose or frequency of an NSID	Corrected prohibited medication rules for the first year of the study
Section 8.2.6 Clinical Safety Laboratory Assessments	See Section 10.2 for the list of…laboratory manual. The actual sample collection date and time will be collected **and included in the central laboratory data transfer.**	Clarified data management procedures
Section 1.3 Schedule of Activities Section 8.2.9.2 ADA Against rHuPH20	Footnote s in Schedule of Activities If no sample was taken, the reason will be recorded ~~in the relevant section of the eCRF~~.	
Section 1.3 Schedule of Activities	Footnote s in Schedule of Activities Titers of ADA and the presence of NAbs against efgartigimod will be measured in serum. Blood samples for plasma titer levels of ADA and NAbs against rHuPH20 will also be taken. **A titer for ADA and the presence of NAbs against PH20 must be measured at study entry for participants coming from ARGX-113-1705.**	Ensured immunogenicity sampling for participants entering this study from study ARGX-113-1705
Section 8.2.9.2 ADA Against rHuPH20	Blood samples will be collected to assess the serum levels of ADA against efgartigimod as indicated in the SoA (Section 1.3), **including a sample taken at study entry for participants coming from study ARGX-113-1705.**	
Section 1.3 Schedule of Activities Section 8.3.1 Time Period and Frequency	Footnote bb of Schedule of Activities Adverse events **(including ongoing AEs from the antecedent studies)**, use of concomitant therapies, use of rescue therapy, medical procedures performed on the participants, and hospitalizations will be collected from	Added requirement for ongoing AE reporting

for Collecting AE and SAE Information	informed consent signature until the last study-related activity. All AEs and SAEs will be collected from the signing of the informed consent form until the EoS or the SFU visit at the time points specified in the SoA (Section 1.3). **Ongoing AEs from the antecedent studies must also be recorded.**	
Section 1.3 Schedule of Activities	Footnote x in the Schedule of Activities Participants who have not previously self-administered efgartigimod PH20 SC in study ARGX-113-2001 will be instructed on self-administration as of TP_1V1 or IP_0V1 in study ARGX-113-2002. Training can continue until the participant or caregiver is ready to administer efgartigimod PH20 SC. **Caregivers must sign the ICF before being trained in IMP administration.**	Added information for a caregiver ICF
Section 1.1 Synopsis, Overall Design Section 4.1 Overall Design	Efgartigimod PH20 SC will be administered… **After signing an informed consent form and** receiving the necessary training, the caregiver can administer the SC injections to the participant.	
Section 10.1.3 Informed Consent Process	**A separate ICF will be issued to all caregivers. Caregivers must sign the ICF before being trained in IMP administration. A copy of the signed and dated caregiver ICF(s) must be provided to the caregiver.** … 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~~.	
Section 1.3 Schedule of Activities	Added row for "**Specialty laboratory tests**" and footnote q **Samples for specialty laboratory tests will be taken at the baseline, the IP_1V1 visit, and the next on-site visit that is at least 4 weeks after the participant's fourth dose (TP_1V4). See Section 10.2.1.**	Added assessments to further investigate the effect of the IMP on lipid metabolism
Section 10.2.1 Specialty Laboratory Tests	**At the visits listed in the SoA, blood will be sampled under fasting conditions for specialty laboratory parameters that may include but not be limited to apolipoprotein B (apoB), lipoprotein A, fibrinogen, von**	

	Willebrand factor, d-dimer, proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9). **These parameters will be analyzed by the central laboratory.**	
Section 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. **The investigator/institution should maintain a record of the location(s) of their respective essential documents, including source documents.** … **The** definition of what constitutes source data can be found in the **investigator source data agreement** ~~data management plan~~.	Clarified guidance around recording the source document locations and the location of the definition of what is considered source data
Section 10.3 Appendix 3: Total Blood Volume Collected From Each Participant	The maximum amount of blood collected from each participant is ~~815 mL~~ **1493.4 mL**.	Updated the maximum blood volume from each participant based on the updated PK sampling schedule
Section 10.6 Appendix 6: Administrative Structure, Table 4	Edited addresses for Covance Bioanalytical Services LLC, Fisher Clinical Services, SGS Life Sciences Added EastHORN Clinical Service and EndPoint as vendors	Updated vendor information
Section 10.7.3.3 Study Protocol Changes	If the COVID-19 pandemic results in participants being unable to visit the site, a home nurse can perform visits that are mandatory to be performed at the site (Section 10.7.3.5). **A home nurse will be a qualified person from either the study site staff or a home health care vendor. If a home nurse is being used, the visits can take place at the participant's home or an alternative location agreed upon by both parties. A participant must consent to performing study visits with a home nurse from the home health care vendor. The use of a home nurse will depend on regional availability. Study staff will follow-up with participants who participate in offsite study visits using the home health care vendor.**	Added information regarding home nurse during the COVID-19 pandemic
Section 10.8.1 Appendix 8 Definitions	Baseline: the data collected prior to the first dose of efgartigimod in ~~the antecedent studies~~	Changed the definition of baseline to align with previous clinical studies

	~~ARGX-113-2001, ARGX-113-1704, or ARGX-113-1705~~ **this study**	
Section 10.9 Protocol Amendment History	Added the following change to Section 8.2.6.2 to Summary of Changes Participants should ~~only~~ be tested **after the IP_0V1 visit** if they have symptoms of COVID-19 or if they were in contact with someone who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements.	Added a previously omitted change to the Summary of Changes from the previous protocol version

10.8.5. Summary of Changes Between Protocol Version 1.0 and Protocol Version 1.5-GER

Overall Rationale for the Changes in Protocol Version 1.5-Germany

The overall rationale for the changes implemented in this protocol version is to conform to the requirements set forth by the competent authorities and ethics committees.

The major changes from Protocol Version 1 compared with Protocol Version 1.5–Germany are summarized in the following table. A double strikethrough indicates deleted text and a bold font indicates added text. Minor editorial changes and document formatting revisions have not been summarized.

Section and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Addition of specific first visit IP_0V1 Marked with footnotes a and b Removed footnote a from TPnV1 and IPnVm visits	Added an obligatory treatment-free visit at the start of the study to test for SARS-CoV-2 before IMP
	Footnote p A nasopharyngeal swab will be performed to sample nasal and throat mucosal cells. **Participants must be tested for SARS-CoV-2 at study entry.** Participants should be tested for SARS-CoV-2 if they have symptoms of COVID-19 or if they were in contact with a person who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements. Participants may be retested as needed.	
	Removal of footnote g ~~These activities are only performed at study entry.~~	

Section and Name	Description of Change	Brief Rationale
	Footnote a The transition from the antecedent studies ARGX-113-1705 or ARGX-113-2001 to study ARGX-113-2002~~ can either~~ will be IP_0V1~~ or TP1V1, depending on the need for retreatment~~.	
Section 1.1 Synopsis	Eligible participants will enter the study on their last visit of the antecedent study, ARGX-113-2001 or ARGX-113-1705. **Participants will enter the study with an IP visit (IP_0V1). Once the results of the SARS-CoV-2 test from that visit are available,** ~~If they are in need of retreatment,~~ the participants will start a TP **if they are in need of retreatment and test negative for SARS-CoV-2**. A TP will consist of an injection of efgartigimod PH20 SC 1000 mg q7d for a total of 4 injections. If the participants are not in need of retreatment, they will~~ start~~ **continue** with ~~an~~ IP visit**s** (**ie,** visit IP_0V~~1~~**2**).	
Section 1.2 Schema	Updated Figure 1 to include IP_0V1 Footnote a Participants will receive efgartigimod PH20 SC 1000 mg q7d for 4 injections. A new TP can be started if the participant is in need of retreatment as determined by the investigator, **has tested negative for SARS-CoV-2,** and at least 28 days have elapsed since the last dose of efgartigimod.	
Section 4.1 Overall Design	At study entry, participants will ~~be evaluated for the~~**start with the IP_0V1 visit, which will include a SARS-CoV-2 test and an evaluation of the participant's** need ~~of~~**for** retreatment. If a participant is in need of retreatment **and has tested negative for SARS-CoV-2**, the **next** visit will become the first visit of the first TP. If a participant is not in need of retreatment, the **next** visit will be an IP visit.	
Section 5.4 Screen Failures	Eligibility to roll over into study ARGX-113-2002 will ~~must~~ be ~~verified~~ **assessed** at the ~~last~~**IP_0V1** visit ~~of the antecedent studies ARGX-113-2001 or ARGX-113-1705, which acts as the first visit of this study~~.	

Section and Name	Description of Change	Brief Rationale
Section 8.2.6.2 SARS-CoV-2 Test	Nasal and throat mucosal cell samples will be collected according to the laboratory manual at the ~~time points~~ **start of the study and as needed after study entry** to ~~be tested~~ test for SARS-CoV-2. Participants should ~~only~~ be tested **after the IP_0V1 visit** if they have symptoms of COVID-19 or if they were in contact with someone who tested positive for SARS-CoV-2, unless local or site regulations have more stringent testing requirements.	
Section 10.2 Appendix 2: Clinical Laboratory Tests, Table 3	Changed the category of the SARS-CoV-2 test from "Unscheduled Test" to "Eligibility Assessment"	
Section 10.7.3.2 Testing for COVID-19	Testing for COVID-19 beyond what is **indicated in Table 1, described in Section 8.2.6.2, and** mandated by the relevant local authorities is not required during the study. … At study entry, if the participant cannot come to the site due to ~~COVID-19 infection or~~ travel restrictions, the ICF can be signed remotely when allowed by local regulations. **A positive SARS-CoV-2 test at study entry is exclusionary.** If a participant is infected with COVID-19 **during the study**, they cannot be (re)treated until they no longer test positive for SARS-CoV-2. ~~These participants can still enter the ARGX-113-2002 study by entering an IP.~~	
Section 5.2 Exclusion Criteria	Exclusion criterion 3 **A positive test for SARS-CoV-2 at IP_0V1**	Added an exclusion criterion for being infected with SARS-CoV-2
Section 5.2 Exclusion Criteria	Exclusion criteria 7 and 8 **The participant stands in any relationship of dependency with the sponsor.** **The participant has been institutionalized due to an official or judicial order.**	Added exclusion criteria to comply with Section 7 (3), No. 4 GCP Regulation and Section 40 Para. 1 S.3 No. 4 AMG (German Drug Law), respectively
Section 10.1.9 Study and Site Start and Closure	For study termination: • Discontinuation of further study intervention development • **An unexpected negative change to the benefit-risk profile of the IMP**	Added additional criteria for study termination based on feedback received from the ethics committee

Section and Name	Description of Change	Brief Rationale
	• **Recommendation of termination by the DSMB** • **A necessary adjustment to the maximum insured sum for the study that is not possible** • **The approvals given by the regulatory agencies and/or IRB/IEC are withdrawn**	
Section 10.5.2.1 Female Contraception for Women of Childbearing Potential	**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.**	Added more information about sexual abstinence as a highly effective method of contraception

10.9. Appendix 9: Summary of Changes Between Protocol Version 1.0 and Protocol Version 2.0

Overall Rationale for the Changes in Protocol Version 2.0

The overall rationale for this amendment includes adding additional optional pharmacokinetic samples from a subset of participants to better evaluate the pharmacokinetics of the investigational medicinal product (IMP), as requested by competent authorities. Additionally, more clinical chemistry laboratory assessments have been added to evaluate the effect of the IMP on lipid panels.

The major changes from protocol version 1.0 compared with protocol version 2.0 are summarized in the following table. A double strikethrough indicates text that was removed and bolded text indicates text that was added. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized.

Section and Name	Description of Change	Brief Rationale
Title Page	Industriepark **Zwijnaarde** 7 ~~B-~~9052 Zwijnaarde **(Ghent)** Belgium	Corrected argenx address
	Added name and affiliation of principal/coordinating investigator Added Investigator's Agreement and signature	Integrated investigator information into protocol
Emergency Contact Information	Added the Emergency Contact Information section with information about SAE reporting	Updated email address and fax number for reporting SAEs
Section 1.1 Synopsis, Objectives and Endpoints Section 3 Objectives and Endpoints	Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), **and AEs of special interest (AESIs)**, and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram results	Edited endpoints for clarity
	[redacted]	
	Added secondary objective and endpoint Objective: **To evaluate the PK of efgartigimod PH20 SC** Endpoint: **Efgartigimod serum concentrations**	Added an objective and endpoint to assess the PK with the additional optional PK assessments.
Section 1.1 Synopsis, Overall Design	**A caregiver is a person of legal age from the participant's social network (eg, family, relatives, friends) introduced by the**	Added the definition of the caregiver

Section and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 10.8.1 Definitions	**participant. After receiving the necessary training, the caregiver can administer the SC injections to the participant.**	
Section 4.1 Overall Design	The total study duration is 2 years from the participant's first visit in this study: • 3-week treatment periods (TPs), repeated as needed based on the clinical effect, **with a maximum of 14 TPs**	Added information contained in the synopsis to the body of the protocol
Section 1.1 Synopsis Section 9.2 Sample Size Determination	"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.	Removed references to the participant's legally authorized or legally acceptable representative that are not appliable to this study.
Section 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	AEs will be reported by the participant (or, when appropriate, by a caregiver, **or** surrogate~~, or the participant's legally authorized representative~~).	
Section 1.3 Schedule of Activities	Added 2 visits, PK1 and PK2, to take place 2 days after the first and fourth dose in a treatment period, respectively. These visits have "Pharmacokinetics" activity row checked. Added footnote c **These are optional visits to collect additional PK samples from consenting participants. These additional visits can only be performed when all of the injections of that treatment cycle are given at the site. Sampling will only be performed during a participant's first and/or second treatment cycles.**	Added additional pharmacokinetic sampling visits to meet competent authority request for more PK sampling
Section 8.4 Pharmacokinetics	**Efgartigimod concentrations will be measured in all participants at study entry and 1 week after the last injection of each treatment cycle.** ~~The following PK parameters will be measured: concentration observed predose (C_{trough}) of efgartigimod PH20 SC~~ **To characterize anticipated peak concentrations, efgartigimod concentrations will also be measured in a subset of at least 12 participants who consent to additional sampling. These participants will perform additional on-site visits 2 days after their**	

Section and Name	Description of Change	Brief Rationale
	first and fourth injections in a treatment cycle. These additional visits can only be performed when all of the injections in a treatment cycle are given at the site. This sampling may only be performed during a participant's first and/or second treatment cycles.	
Section 1.3 Schedule of Activities	End of study visit study day changed ~~728~~730	Corrected the number of days to accurately reflect the study duration
	Footnote b This visit must always be performed at the site. **All other visits can be performed by phone if IMP administration occurs at home.**	Clarified which visits are phone visits
	Footnote y The first dose administration of all TPs…may be performed at home. **When IMP administration is performed at home, the associated visit will be performed by phone.**	
	Footnote u The PK assessments will only be taken at TP_1V1. The assessment should be performed predose.~~ only at TP_1V1.~~	Clarified the timing of the PK sampling
	Added row for "**Blood sampling**"	Rearranged the Schedule of Activities to group the blood sampling together
Section 1.1 Synopsis, Intervention Groups and Duration Section 1.2 Schema Section 1.3 Schedule of Activities	Footnote c in Figure 1 Footnote d in Figure 2 Footnote f in Schedule of Activities The study will last for 2 years **from the participant's first visit in this study.**	Clarified study duration
Section 1.3 Schedule of Activities Section 6.6 Continued Access to Study Intervention After the End of the Study	Footnote f in Schedule of Activities If efgartigimod becomes commercially available **for patients with gMG** or available through another patient program **for gMG**, participants will have the choice to switch to 1 of these options after 1 year of participation in this long-term safety study. **No treatment-free follow-up will be performed in this study, except for participants who do not want to continue receiving efgartigimod.**	Clarified procedures for continued access to IMP after the study

Section and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities Section 6.4 Study Intervention Compliance	Footnote x in Schedule of Activities Participants who have not previously self-administered…only be performed on-site. **At every on-site visit, the study staff must review the administration log and patient diary with the participant.**	Added the instruction to review the administration log and patient diary to check for compliance and adverse events
Section 1.3 Schedule of Activities	Footnote p Blood samples for clinical laboratory (hematology/clinical chemistry and FSH, if applicable) safety assessments will be collected. On dosing days, the samples will be taken predose. Participants need to be fasted (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.	Clarified policy on taking permitted medications before each sampling. Aligned fasted definition with previous studies
Section 1.3 Schedule of Activities Section 5.3 Lifestyle Considerations	Footnote p in the Schedule of Activities Participants will need to be fasted for each on-site visit **at which safety laboratory assessments will be performed**. Fasted is defined as no food or drink ~~except for water,~~ for at least 8 hours prior to the visit**. Permitted medications that the participant normally takes can be taken as usual before a visit.**	
Section 8.2.6.1 Hematology, Clinical Chemistry, and Urinalysis	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 for up to 4 hours prior to the assessment.~~	
Section 8.2.9.1 ADA Against Efgartigimod Section 8.2.9.1 ADA Against rHuPH20 Section 8.2.10 Vaccine Antibody Titers and PBMCs	**The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual.**	Added the location of the instructions for sampling
Section 1.3 Schedule of Activities Section 8.2.10 Vaccine Antibody Titers and PBMCs	Footnote r in the Schedule of Activities Additional blood samples (serum/peripheral blood mononuclear cells [PBMCs]) may need to be taken for additional/optional/future**/vaccination** research…occurred. In addition,~~ if a participant consents to it,~~ a whole-blood sample to isolate PBMCs will be collected **at study entry and**	Clarified that participants will have the option to consent to both serum and PBMC samples instead of one or the other. Added PBMC sampling at study entry

Section and Name	Description of Change	Brief Rationale
	then approximately every 3 months throughout the study during a scheduled on-site visit, regardless of the vaccines a participant has received.	
Section 1.3 Schedule of Activities	Footnote bb in the Schedule of Activities Adverse events, use of concomitant therapies, use of rescue therapy, medical procedures performed on participants, and hospitalizations will be collected informed consent signature until the last study-related activity. All available vaccination history for participants rolling over from ARGX-113-1705 ~~will be captured as a part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the study.~~ **should be recorded in the eCRF. All vaccines received during the study should be recorded as concomitant medication.** See Section 6.8 and Section 8.3	Clarification on the recording of vaccination history and vaccines received during the study.
Section 8.2.6 Clinical Safety Laboratory Assessments	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 **and an** SAE, then **it** ~~the outcomes~~ must be recorded **on the SAE form.**	Simplified the text by removing redundant information
Section 8.2.6.1 Hematology, Clinical Chemistry	~~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 for 8 hours.~~ ~~• Blood samples for safety assessments will be collected according to the laboratory manual.~~ ~~• The samples will be analyzed at the central laboratory.~~	
Section 5.1 Inclusion Criteria	Criterion 3.a. Male participants:	Updated contraceptive requirement to reflect new reproductive toxicity data

Section and Name	Description of Change	Brief Rationale
	Male participants are not allowed to donate sperm from signing the ICF ~~through 90 days after the last dose of IMP~~ **until the end of the study.**	
Section 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 will be provided** with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.	Edited the information regarding supplying the IMP for clarity
Section 6.4 Study Intervention Compliance	Errors that are identified…without supervision. ~~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.	Clarified administration error text.
Section 1.2 Schema, Figures 1 and 2 Section 6.5.1 Retreatment Criteria	Footnote a in the Schema **There must be at least 7 weeks left in the study for the participant, so that a full TP and IP can be performed.**	Added a retreatment condition to restrict starting treatment periods near the end of the study so that participants can complete a full treatment cycle
Section 6.7 Treatment of Overdose	~~A participant must not miss more than 2 consecutive doses and must not miss more than 10% of the total planned doses. Furthermore,~~ There must be at least 3 days between 2 consecutive doses.	Removed unnecessary restriction on missing doses
Section 6.8.1 Prior Medication and Procedures	For participants rolling over from ARGX-113-1705, all available vaccination history ~~must be collected~~ **should be recorded in the eCRF. Any vaccination information that the participant or their caregiver can remember should be recorded in the eCRF with the brand name of the vaccine and date of vaccination, if possible.**	Added vaccination history collection information for participants entering the study from study ARGX-113-1705
Section 6.8.2 Permitted Concomitant Medication and Procedures	Any vaccination ~~within 28 days of study entry up until the end of the study~~ **during the** study should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration.	Updated information on recording received vaccination so information can be used in a separate analysis

Section and Name	Description of Change	Brief Rationale
Section 6.8.3 Prohibited Medications and Procedures	In the first year of the study, participants are NOT allowed to do any of the following: … ~~change~~ **increase** the dose or frequency of an NSID	Corrected prohibited medication rules for the first year of the study
Section 8.2.6 Clinical Safety Laboratory Assessments	See Section 10.2 for the list of…laboratory manual. The actual sample collection date and time will be collected **and included in the central laboratory data transfer.**	Clarified data management procedures
Section 1.3 Schedule of Activities Section 8.2.9.2 ADA Against rHuPH20	Footnote s in Schedule of Activities If no sample was taken, the reason will be recorded~~ in the relevant section of the eCRF~~.	
Section 1.3 Schedule of Activities	Footnote s in Schedule of Activities Titers of ADA and the presence of NAbs against efgartigimod will be measured in serum. Blood samples for plasma titer levels of ADA and NAbs against rHuPH20 will also be taken. **A titer for ADA and the presence of NAbs against PH20 must be measured at study entry for participants coming from ARGX-113-1705.**	Ensured immunogenicity sampling for participants entering this study from study ARGX-113-1705
Section 8.2.9.2 ADA Against rHuPH20	Blood samples will be collected to assess the serum levels of ADA against efgartigimod as indicated in the SoA (Section 1.3), **including a sample taken at study entry for participants coming from study ARGX-113-1705.**	
Section 1.3 Schedule of Activities Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Footnote bb of Schedule of Activities Adverse events **(including ongoing AEs from the antecedent studies)**, use of concomitant therapies, use of rescue therapy, medical procedures performed on the participants, and hospitalizations will be collected from informed consent signature until the last study-related activity. All AEs and SAEs will be collected from the signing of the informed consent form until the EoS or the SFU visit at the time points specified in the SoA (Section 1.3). **Ongoing AEs from the antecedent studies must also be recorded.**	Added requirement for ongoing AE reporting
Section 1.3 Schedule of Activities	Footnote x in the Schedule of Activities Participants who have not previously self-administered efgartigimod PH20 SC in study	Added information for a caregiver ICF

Section and Name	Description of Change	Brief Rationale
	ARGX-113-2001 will be instructed on self-administration as of TP_1V1 or IP_0V1 in study ARGX-113-2002. Training can continue until the participant or caregiver is ready to administer efgartigimod PH20 SC. **Caregivers must sign the ICF before being trained in IMP administration.**	
Section 1.1 Synopsis, Overall Design Section 4.1 Overall Design	Efgartigimod PH20 SC will be administered… **After signing an informed consent form and** receiving the necessary training, the caregiver can administer the SC injections to the participant.	
Section 10.1.3 Informed Consent Process	**A separate ICF will be issued to all caregivers. Caregivers must sign the ICF before being trained in IMP administration. A copy of the signed and dated caregiver ICF(s) must be provided to the caregiver.** … 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~~.	
Section 1.3 Schedule of Activities	Added row for "**Specialty laboratory tests**" and footnote q **Samples for specialty laboratory tests will be taken at the baseline, the IP_1V1 visit, and the next on-site visit that is at least 4 weeks after the participant's fourth dose (TP_1V4). See Section 10.2.1.**	Added assessments to further investigate the effect of the IMP on lipid metabolism
Section 10.2.1 Specialty Laboratory Tests	**At the visits listed in the SoA, blood will be sampled under fasting conditions for specialty laboratory parameters that may include but not be limited to apolipoprotein B (apoB), lipoprotein A, fibrinogen, von Willebrand factor, d-dimer, proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9).** **These parameters will be analyzed by the central laboratory.**	
Section 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. **The investigator/institution should maintain**	Clarified guidance around recording the source document locations and the location of the

Section and Name	Description of Change	Brief Rationale
	a record of the location(s) of their respective essential documents, including source documents. … **The** definition of what constitutes source data can be found in the **investigator source data agreement** ~~data management plan~~.	definition of what is considered source data
Section 10.3 Appendix 3: Total Blood Volume Collected From Each Participant	The maximum amount of blood collected from each participant is ~~815 mL~~ **1493.4 mL**.	Updated the maximum blood volume from each participant based on the updated PK sampling schedule
Section 10.5.2 Appendix 5: Contraception Guidance	**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.**	Provided more information about sexual abstinence as a contraception method
Section 10.6 Appendix 6: Administrative Structure, Table 4	Edited addresses for Covance Bioanalytical Services LLC, Fisher Clinical Services, SGS Life Sciences Added EastHORN Clinical Service and EndPoint as vendors	Updated vendor information
Section 10.7.3.3 Study Protocol Changes	If the COVID-19 pandemic results in participants being unable to visit the site, a home nurse can perform visits that are mandatory to be performed at the site (Section 10.7.3.5). **A home nurse will be a qualified person from either the study site staff or a home health care vendor. If a home nurse is being used, the visits can take place at the participant's home or an alternative location agreed upon by both parties. A participant must consent to performing study visits with a home nurse from the home health care vendor. The use of a home nurse will depend on regional availability. Study staff will follow-up with participants who participate in offsite study visits using the home health care vendor.**	Added information regarding home nurse during the COVID-19 pandemic
Section 10.8.1 Appendix 8 Definitions	Baseline: the data collected prior to the first dose of efgartigimod in ~~the antecedent studies~~	Changed the definition of baseline to align with previous clinical studies

Section and Name	Description of Change	Brief Rationale
	~~ARGX-113-2001, ARGX-113-1704, or ARGX-113-1705~~ **this study**	

11. REFERENCES

1. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve.* 2008;37(2):141-149.
2. Wendell LC, Levine JM. Myasthenic crisis. *Neurohospitalist*. 2011;1(1):16-22.
3. Gilhus NE. Myasthenia gravis. *N Engl J Med*. 2016; 375:2570-2581.
4. Knowles SP, Printz MA, Kang DW, LaBarre MJ, Tannenbaum RP. Safety of recombinant human hyaluronidase PH20 for subcutaneous drug delivery. *Expert Opin Drug Deliv.* 2021;18(11):1673-1685.
5. Ikeda S, Shiroiwa T, Igarashi A, et al. Developing a Japanese version of the EQ-5D-5L value set. *J Natl Inst Public Health*. 2015; 64(1):47-55.
6. Japanese Society of Neurology. Myasthenia gravis clinical practice guideline 2014. Japanese Society of Neurology website, 2014. Available at: https://www.neurology-jp.org/guidelinem/mg.html
7. FDA. Immunogenicity testing of therapeutic protein products—developing and validating assays for anti-drug antibody detection. Guidance for Industry. U.S. Food and Drug Administration website, 2019. Available at: https://www.fda.gov/media/119788/download
8. Center for Drug Evaluation and Research (CDER). Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. US Department of Health and Human Services, Food and Drug Administration (FDA) website. Draft Guidance for Industry, Revision 1, August 2012. Accessed 16 Nov 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-suicidal-ideation-and-behavior-prospective-assessment-occurrence-clinical-trials

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