Protocol Title:

A Phase 3b, Randomized, Open-label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit in Patients With Generalized Myasthenia Gravis

Short Title:

An open-label study to investigate the clinical efficacy of different dosing regimens of efgartigimod IV in patients with generalized myasthenia gravis

Protocol Number: ARGX-113-2003

Version number: 2.0

Compound: Efgartigimod IV (ARGX-113)

Study Phase: 3b

Acronym: ADAPT NXT

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PROTOCOL SIGNATURE PAGE

Sponsor's (argenx) Approval

Protocol Title:	
Protocol Number	
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-113-2003.

Title: A Phase 3b, Randomized, Open-label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit 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 will not be disclosed, except 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 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 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 can lead to the termination of my participation as an investigator for this study.

I understand that the sponsor can decide to suspend or prematurely terminate the study at any time for any reason; such a decision will be communicated to me in writing. Conversely, if 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 hand print or type)	_____ _____ _____ _____
Signature	_____
Date	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Global protocol document history	Date
Amendment 1 v2.0	05 May 2023
Original v1.0	06 Jul 2021

Amendment 1 (05 May 2023)

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

Overall Rationale for the Amendment

The overall rationale for this amendment is to remove vaccination samples and specialty laboratory tests and to incorporate information based on a clarification letter dated 07 Mar 2022. Country-specific protocols from France and Germany have been incorporated into the country-specific requirements section, and this v2.0 amendment supersedes the country-specific amendments. Language has been updated for clarity throughout, as indicated in the summary of changes. A strikethrough indicates deleted text, and bold text indicates added text. Minor editorial changes related to typos, style, and formatting inconsistencies are not presented.

Section	Description of change	Brief rationale
8.2.11. Vaccine Antibody Titers and PBMCs 1.3. Schedule of Activities, Table 1; Table 2	"Vaccine Antibody Titers and PBMCs" section and "Vaccination antibody Titers and PBMCs" lines in Schedule of Activities tables were removed.	Efgartigimod does not affect the ability to mount an immune response to antigen challenges. The optional blood sample collection for vaccine antibody titers and peripheral blood mononuclear cells are no longer needed.

1.3. Schedule of Activities, Table 1, footnote q; Table 2, footnotes e and n 2.3.1. Risk Assessment 10.4.2.1. Female Contraception for Women of Childbearing Potential 10.7.1. France-specific Requirements 10.7.2. Germany-specific Requirements	For France, requirements that all efgartigimod IV infusions must be administered at the sites and that participants must be monitored for at least 1 hour after the end of the infusion (instead of 30 min) were added. For Germany, an exception was added that only highly effective contraceptive methods must be used.	All previous country-specific protocols were merged into this global v2.0 protocol.
5.1. Inclusion Criteria 7.1 10.4.1. Women of Childbearing Potential 10.4.2.1. Female Contraception for Women of Childbearing Potential 10.4.2.2. Male Contraception	The definition of WOCBP and requirements for female contraception were updated. The requirements for male contraception were removed.	The inclusion criteria and contraception sections were updated to align with changes to contraception requirements based on more recent data for efgartigimod. References to country-specific requirements were also added.
1.1. Synopsis 6.6. Dose Modification 6.9.2. Permitted Concomitant Medication and Procedures	Added: **The dose of the concomitant gMG therapy should not be changed during the transition between the q2w and q3w dosing regimens."**	Information was added for when dose of concomitant gMG therapy can be changed to remove bias in the measurements for transitioning between dosing regimens and/or tapering concomitant MG therapy.
1.1. Synopsis	Prohibited medication requirements were updated to specify that a change in gMG	Requirements for discontinuation were clarified

1.3. Schedule of Activities, Table 1, footnote a; Table 2 footnote c 6.9.3. Prohibited Medications and Procedures 7.1.1. Permanent Discontinuation 7.2. Participant Discontinuation/ Withdrawal From the Study	therapy in part A will not lead to study discontinuation but will be reported as a protocol deviation. In cases where the participant receives prohibited medication and is withdrawn from the study, it was specified that the ET visit must be done within 7 days of the early discontinuation decision rather than 7 days from the last dose. "ET" visit was also changed from "end of treatment visit" to "early termination visit." It was clarified that there are no restrictions for part B.	by updating when prohibited medications cause a discontinuation in part A, what prohibited treatments do not result in study discontinuation, and rewording early termination (ET) visit requirements, as well as better differentiating between an ET and an end of study (EoS) visit.
1.1. Synopsis 1.2. Schema 1.3. Schedule of Activities, Table 1, footnote a; Table 2 footnote c 4.1. Overall Design 7.2. Participant Discontinuation/Withdrawal From the Study	An SFU visit was added and should be performed for all participants. This may be a phone call assessing only AEs and concomitant therapy and procedures if a participant continues efgartigimod via commercial access or through another patient access program for gMG. The overall study length was updated to 138 weeks throughout to account for this change.	A SFU visit should be performed if possible for all participants, given there is no open label extension planned for this study and no intertreatment follow-up period longer than 2 weeks. However, this can be a remote, SFU visit for participants who continue IMP through other sources.
1.3 Schedule of Activities, Table 1, footnote m; Table 2 footnote h 8.2.7. Lipid Metabolism 10.2.2. Specialty Laboratory Tests	All specialty lipid tests were removed, deleting Sections 8.2.7 and 10.2.2.	Per the 07 Mar 2022 administration letter, lipid laboratory tests were removed to reduce the burden for the participant, as new data demonstrate no impact of efgartigimod on lipid results.
4.1. Overall Design 5.1. Inclusion Criteria 3.1	AChR-Ab requirements were updated to clarify that historical results can be used for AChR screening criteria.	Text was added to ensure participant eligibility can still be determined when sites encounter laboratory delays in

10.2. Appendix 2: Clinical Laboratory Tests, Table 8: Protocol-Required Safety Laboratory Tests: Other screening tests	AChR-Ab serology was added as a protocol-required safety laboratory test under “Other screening tests”.	providing AChR-Ab test results.
8.2.6.3. Follicle-Stimulating Hormone Levels 10.2. Appendix 2: Clinical Laboratory Tests, Table 8: Protocol-Required Safety Laboratory Tests: Other screening tests, Abbreviations	Female participants was replaced with “WOCBP.” FSH testing requirements were updated to exclude surgically sterilized female participants.	FSH testing requirements were updated to exclude FSH testing in surgically sterilized female participants.
10.2. Appendix 2: Clinical Laboratory Tests, Table 8: Protocol-Required Safety Laboratory Tests: Other screening tests, Abbreviations	“INR" was changed to “**PTT,** INR.” Old terms (“SGOT” and “SGPT”) were deleted.	“PTT” to “INR” were added to align with laboratory specifications, as PTT is a measured parameter used to calculate INR. Old terms (“SGOT” and “SGPT”) were deleted for clarity.
1.1. Synopsis 1.3. Schedule of Activities, Table 1 footnote q; Table 2 footnote n	Text was updated to require the first 3 infusions of the first TP to be administered at the investigative site, before allowing off-site administration. W1 and W2 were split from W3 to indicate required onsite visits for W1 and W2 in the SoA.	On-site visit requirements were updated to improve participant safety by decreasing the risk of anaphylactic reactions occurring at home.
10.1.8. Data Quality Assurance	The first paragraph of the data quality assurance section was updated to following text: All participant data relating to the study will be recorded on ~~printed or~~ eCRF**s** unless transmitted to the sponsor **(**or **its** designee**)**	Recording of participant data was clarified in order to align with current argenx policy.

	electronically (eg, laboratory data) or **via paper SAE forms**. The investigator is responsible for verifying that data entries are **complete**, accurate, and ~~correct~~**verifiable** by electronically signing the eCRF.	
10.1.4. Recruitment Strategy	A section specifying the recruitment strategy was added.	The recruitment strategy section was added to comply with EU-CTR requirements.
1.3. Schedule of Activities, Table 1 footnote j	Footnote "j" was added for [redacted] Day 1, and the following footnote wording was added: **Baseline assessment refers to background medication administered for gMG.**	The baseline assessment definition was clarified.
9.2. Analysis Sets, Table 6	"W20" was updated to "W21."	Part A ends after all predose assessments have been performed at the W21 visit, and this update aligns with the SAP.
1.1. Synopsis	The definition of "enrolled" was updated: "*Enrolled* means ~~a~~**the** participant~~'s, or their legally acceptable representative's, agreement~~ **agrees** to participate in ~~a~~**the** clinical study ~~following completion of~~**by completing** 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. A participant will be considered enrolled if the informed consent is not withdrawn before participating in any study activity after screening~~."	The definition of "enrolled" was clarified in order to align with argenx policy.
2.3. Benefit/Risk Assessment 2.3.1. Risk Assessment	The benefit/risk assessment text and risk assessment text (including Table 3) have been updated to align with the most recent data for efgartigimod.	The benefit/risk section was updated to align with the most recent data for efgartigimod.

2.3.2. Benefit Assessment 5.2. Exclusion Criteria 1.1	The benefit assessment section was removed. Exclusion criterion 1 was updated to align with the updated risk section for infections.	
5. Study Population	Removed reference to "recruitment" in describing policy on prospective protocol deviations.	The text describing wording on protocol deviations to align with argenx policy.
5.4. Screen Failures	Updated the definition of a screen failure: A screen failure occurs when a participant who ~~consents to participate in~~**has signed** the ~~clinical study~~**ICF** is not ~~subsequently entered in the study~~**assigned to IMP**. A minimal set of screen failure information **(demography, screen failure details, eligibility criteria, and SAE reports)** 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~~**and address** regulatory ~~authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE~~**authority queries**.	The definition of screen failure was clarified and reporting requirements for screening failure were included.
6. Study Intervention(s) and Concomitant Therapy 6.2.1. Preparation	The definition of study intervention was updated: ~~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.~~**All IMP is manufactured according to Good Manufacturing Practice regulations.** This wording was removed from Section 6.2.1.	Text describing the study intervention was condensed to avoid repetition in multiple sections.

6.1. Study Intervention(s) Administered, Table 4	The IMP table was updated to more clearly state dosing details.	IMP dosing was clarified.
9.3.3. Other Endpoint(s)/Estimand(s) Analysis	Added: **Population PK and PD analyses may be performed and will be reported separately.**	Population PK and PD analyses may be done, and it was clarified how they will be reported.
6.2.3. Storage	Removed: ~~The investigator will be provided with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.~~	Text was condensed to only describe storage of IMP in Section 6.2.3.
6.2.4. Accountability	Removed: ~~Detailed instructions on accountability of the IMP will be included in the pharmacy manual.~~	Text was condensed to only describe responsibilities for IMP accountability.
6.3. Assignment of IMP 6.4. Measures to Minimize Bias: Randomization and Blinding	Section 6.4 was added to address measures taken to minimize selection bias.	Information was added to describe how selection bias will be reduced by the use of central randomization.
6.6. Dose Modification	Added: **The maximum total efgartigimod dose per efgartigimod infusion is 1200 mg for participants weighing ≥ 120 kg. The IMP weight-based dose will be recalculated if a participant's weight has changed by more than or equal to 10% from baseline.**	Information was added regarding the maximum dose of total IMP to be given.
1.1. Synopsis 6.7. Continued Access to Study Intervention	The text was changed: At the end of the study, argenx **cannot guarantee continued access for participants but** will comply with all local	The policy on continued access was updated to comply with recent updates needed,

After the End of the Study	**laws and** regulations ~~for ensuring continued access to IMP medically identified as essential~~.	given efgartigimod regulatory approval.
6.8. Treatment of Overdose	The text was updated to identify how an overdose should be handled.	Information on the handling of an overdose was updated and expanded.
1.1. Synopsis 6.9.4. Rescue Medication 7.1.1. Permanent Discontinuation	The requirement that a maximum of 3 rescue treatments are allowed per year was added, along with an explanation that more than 3 rescue therapy treatments will trigger IMP discontinuation..	Limiting the number of rescue treatments will avoid having participants who do not benefit from IMP continue the study.
7. IMP Discontinuation and Participant Discontinuation/Withdrawal 7.1. IMP Discontinuation 7.1.1. Permanent Discontinuation 7.1.2. Temporary Discontinuation 7.2 Participant Discontinuation/Withdrawal From the Study	Section 7 was renamed: Section 7: ~~Discontinuation of Study Intervention~~**IMP Discontinuation and Participant Discontinuation/Withdrawal** The section reference was updated for site and study discontinuation. Section 7.1. was renamed: Section 7.1: ~~Discontinuation of Study Intervention~~**IMP Discontinuation** Subsection 7.1.1 Permanent Discontinuation was created: **Section 7.1.1: Permanent Discontinuation** Permanent discontinuation was defined as: **Permanent discontinuation of IMP occurs when the participant stops receiving IMP before the end of the study and does not resume receiving IMP. The participant also must not have withdrawn informed consent.** The following text was added:	The difference between permanent and temporary IMP discontinuation, and that permanent IMP discontinuation leads to study discontinuation, was clarified.

	The investigator will document the primary reason for early discontinuation of IMP. **Unless consent from the study has been withdrawn, the participant will discontinue the study (refer to Section 7.2) and attend an ET visit and an SFU visit. Study sites will attempt to perform the ET visit within 7 days of the early discontinuation decision. The SFU visit will occur 60 ±3 days after the participant's final IMP administration.** **The following circumstances will result in the permanent discontinuation of IMP:** • **Participant becomes pregnant or intends to become pregnant (refer to Section 8.2.7).** • **Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed).** • **Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of NCI-CTCAE grade 4 that is considered related to IMP by the sponsor.** • **Participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship to the IMP.** • **Participant receives a prohibited medication or substance (Section 6.9).**	

	• **Participant receives more than 3 rescue therapy treatments per year** The temporary discontinuation section was updated: **7.1.2 Temporary Discontinuation** ~~Participants may have a temporary discontinuation of the IMP if necessary, without being required to discontinue early from the study. Participants can temporarily discontinue the IMP because of a temporary medical condition that puts them at undue risk (ie, symptoms of infection, abnormalities in safety laboratory assessments). These participants may still be eligible for additional doses of IMP. If a dose cannot be administered within a visit window as specified in the SoA, then that dose will be missed, and the treatment interruption and the reason for the missed dose(s) will be documented. All reasonable efforts will be made to prevent missed doses. The next planned dose can be administered to the participant at the next scheduled dosing visit if the investigator determines that the undue risk has been resolved. The participant must continue to participate in all scheduled visits while the IMP is temporarily discontinued.~~ **Temporary discontinuation of IMP occurs when the participant discontinues receiving IMP before the end of the study and resumes once the cause for the discontinuation has been resolved.** **Reasons for temporary discontinuation may include an AE that meets the following criteria:** • **Any SAE considered related to IMP by the sponsor**	

	• **Clinically significant active infection considered related to the IMP by the sponsor** **7.2 Participant Discontinuation/Withdrawal From the Study** The following bullet was added to the reasons participants must discontinue the study: • **IMP is permanently discontinued (refer to Section 7.1.1).**	
8.3.4. Pregnancy	The last bullet of the section was updated to require that a pregnant participant discontinue IMP rather than the study.	The text was updated to clarify that pregnancy results in IMP discontinuation
8. Study Assessments and Procedures	References to the sponsor for discontinuation, as well as screening evaluations, timing of assessments and procedures, and source documents, were removed.	References to the sponsor in discontinuing IMP were removed to align with argenx policy. Additional information regarding screening evaluations, timing of assessments and procedures, and source documents were removed due to redundancy.
1.3. Schedule of Activities, Table 1 footnote p; Table 2 footnote k 8.4. Pharmacokinetics	A clarification was added that only 1 PK sample will be taken on nondosing days.	It was clarified that 2 samples are taken only on dosing days, and 1 on nondosing days.
4.3. Justification for Dose	The text was updated: Furthermore, ~~this~~**the** dose **of 10 mg/kg IV** has been well-tolerated and has had a favorable risk-benefit profile in clinical studies conducted to date. In ongoing clinical studies in other indications in which ~~the~~IMP is being administered weekly or	The dose justification was updated to align with most recent data for efgartigimod.

	q2w (ARGX-113-1801, ARGX-113-1803, ARGX-113-1701), no SAEs ~~have been assessed~~**were reported** as related to efgartigimod.~~As of~~ by the ~~data cutoff on 25 March 2020, a study in patients with pemphigus (ARGX-113-1701) supports the favorable risk-benefit profile~~**investigator.**[4]	
8.2. Safety Assessments	Added: **Safety measures will be assessed before IMP administration unless otherwise stated.** **At screening, clinically significant abnormalities in any safety assessment related to preexisting conditions will be reported as medical history. New abnormal or worsened preexisting conditions observed after screening that the investigator considers clinically significant will be reported as an AE.**	Requirements were added for reporting clinically significant abnormalities at screening to differentiate between medical history and an AE.
8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting	The definition of an AESI was added, and what constitutes an AE was clarified.	The definition of an AESI was added to clarify the differences between an AE and AESI.
8.3.6. Adverse Events of Clinical Interest 8.3.6.1. Infusion/Injection-Related Reactions	Section 8.3.6 AEs of Clinical Interest section and Section 8.3.6.1 Infusion/Injection-Related Reactions were added, containing the following text: **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 or IV injection, injection- or infusion-related reactions can occur during or after administration.**	The definition of AEs of clinical interest (infusion/injection-related reactions) was added to differentiate between AEs, AESIs, and AEs of clinical interest.

	Overall, the frequency of infusion/injection-related reactions in clinical studies has been low. **The efgartigimod IB provides more information on infusion-/injection related reactions.**	
10.1.10. Study and Site Start and Closure	Text was added to indicate that accessibility of IMP for participants outside of the study may lead to site termination.	Text was added to clarify that if IMP becomes available for participants outside of the study at a site, this may lead to site termination.
9. Statistical Considerations	The text was updated: ~~A detailed and comprehensive statistical analysis plan~~ ~~(~~**The** SAP~~)~~ will be ~~written and signed off~~ **finalized** before ~~an interim or final analysis~~ database lock **and includes a more technical and detailed description of the statistical analyses described in this section.**	The details of SAP finalization were clarified.
4.4. End of Study Definition	The following text was edited: The end of the study is defined as ~~the last visit of~~the last participant**'s** ~~in the study~~ **last visit**.	The end of study definition was edited for clarity.
10.1.1. Regulatory and Ethical Considerations	The text in the last bullet of section was updated: Providing oversight of ~~the~~ **study** conduct ~~of the study~~ at the site and ~~adherence~~**adhering** to requirements of ~~21 GFR,~~ICH guidelines, the IRB/IEC, ~~European regulation 536/2014~~**and local laws and regulations** for clinical studies~~(if applicable)~~, and all other applicable local regulations.	Regulatory requirements for study conduct oversight and adhering to requirements of ICH guidelines were clarified.
10.1.5. Data Protection	The text below was added: **The contract between sponsor and study sites specifies responsibilities of the**	Text was added to ensure compliance with current General Data Protection Regulation requirements.

	parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties. **Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.**	
10.1.7. Dissemination of Clinical Study Data	The text below was added: **The sponsor will register and disclose the clinical study results as required by law.**	Text was added to clarify requirements for results disclosure.
10.1.11. Publication Policy	The publication policy was changed: ~~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 before submission for publication or presentation. Study participant identifiers will not be used in the publication of results.~~ **The results of this study can be published or presented at scientific meetings. If so, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.**	Text was changed to clarify the publication policy.
10.2.1.1. Hepatitis B Virus, Table 9	Table 9 was updated to define chronic HBV infection with impaired liver function, and a reference was updated.	The definition of a HBV infection was added for clarity.
10.2.1.2. Hepatitis C Virus, Table 10	Table 10 was updated to define exclusionary HCV infection.	The definition of a HCV infection was added for clarity.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information 8.3.5. Adverse Events of Special Interest 10.3.4. Reporting of SAEs	AESIs were added to SAE reporting, and the instructions for recording SAEs were updated. AESIs were defined and the timeframe for reporting clarified, with a reference to temporary IMP interruption also added. Clarified that AEs and SAEs will be collected until the SFU.	The SAE and AESI reporting requirements were clarified.
10.3.3. Recording and Follow-up of AE and/or SAE	Removed text below: ~~New or updated information will be recorded in the originally submitted documents.~~ Updated first paragraph in assessment of causality section to the below text: The investigator is obligated to assess the relationship between ~~study intervention~~**IMP**, study procedures, and each occurrence of each AE/SAE as related or not related.	AE recording processes were clarified.
10.6.2. COVID-19 Risk Mitigation	The text was updated to indicate that testing positive for SARS-CoV-2 may result in temporary discontinuation in alignment with discontinuation requirements.	It was clarified that COVID-19 may not always result in temporary discontinuation.
6.6. Dose Modification	It was clarified that participants in the cyclic arm may transition dosing regimens after, not during, W28.	A typo was corrected.
Title Page, confidentiality statement	The confidentiality statement was updated.	The text was updated to the current argenx confidentiality statement.
Protocol Signature Page	The following text was updated: "[redacted]**, MD, PhD** Chief Medical Officer~~, argenx BV~~"	The current chief medical officer was updated.

5.1. Inclusion Criteria 4.1	"MFGA" was changed to "MGFA".	A typo was corrected.

TABLE OF CONTENTS

PROTOCOL SIGNATURE PAGE 3
PROTOCOL AMENDMENT SUMMARY OF CHANGES 5
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 27
1. PROTOCOL SUMMARY 30
1.1. Synopsis 30
1.2. Schema 38
1.3. Schedule of Activities 40
2. INTRODUCTION 47
2.1. Study Rationale 47
2.2. Background 47
2.3. Benefit/Risk Assessment 48
2.3.1. Risk Assessment 48
2.3.2. Overall Benefit/Risk Conclusion 49
3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS 50
4. STUDY DESIGN 54
4.1. Overall Design 54
4.2. Scientific Rationale for Study Design 55
4.3. Justification for Dose 55
4.4. End of Study Definition 55
5. STUDY POPULATION 56
5.1. Inclusion Criteria 56
5.2. Exclusion Criteria 56
5.3. Lifestyle Considerations 58
5.4. Screen Failures 58
5.5. Criteria for Temporarily Delaying Administration of Study Intervention 58
6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 59
6.1. Study Intervention(s) Administered 59
6.2. Preparation, Handling, Storage, and Accountability 59
6.2.1. Preparation 59
6.2.2. Handling 60
6.2.3. Storage 60

6.2.4. Accountability....60
6.3. Assignment to IMP....60
6.4. Measures to Minimize Bias: Randomization and Blinding....60
6.5. Study Intervention Compliance....60
6.5.1. Handling Missed Doses of the IMP....61
6.5.2. Protocol Deviations....61
6.6. Dose Modification....61
6.7. Continued Access to Study Intervention After the End of the Study....62
6.8. Treatment of Overdose....62
6.9. Concomitant Therapy....62
6.9.1. Prior Medications and Procedures....63
6.9.2. Permitted Concomitant Medication and Procedures....63
6.9.3. Prohibited Medications and Procedures....63
6.9.4. Rescue Medication....64
7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL....65
7.1. IMP Discontinuation....65
7.1.1. Permanent Discontinuation....65
7.1.2. Temporary Discontinuation....65
7.2. Participant Discontinuation/Withdrawal From the Study....65
7.3. Lost to Follow-up....66
8. STUDY ASSESSMENTS AND PROCEDURES....68
8.1. Efficacy Assessments....68
8.1.1. Pharmacodynamics....68
8.1.2. MG-ADL....68
8.1.3. [redacted]68
8.1.4. [redacted]69
8.1.5. [redacted]69
8.1.6. [redacted]70
8.2. Safety Assessments....70
8.2.1. Demographic Characteristics....70
8.2.2. Medical and Surgical History....70

8.2.3. Physical Examinations 70
8.2.4. Vital Signs 71
8.2.5. Electrocardiograms 71
8.2.6. Clinical Safety Laboratory Tests 71
8.2.6.1. Hematology, Clinical Chemistry, and Urinalysis 72
8.2.6.2. Virus Serology 72
8.2.6.3. Follicle-Stimulating Hormone Levels 72
8.2.6.4. SARS-CoV-2 Test 72
8.2.7. Pregnancy Testing 72
8.2.8. Immunogenicity 73
8.2.9. Suicidal Ideation and Behavior Risk Monitoring 73
8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting 73
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 74
8.3.2. Method of Detecting AEs and SAEs 74
8.3.3. Follow-up of AEs and SAEs 74
8.3.4. Pregnancy 75
8.3.5. Adverse Events of Special Interest 76
8.3.6. Adverse Events of Clinical Interest 76
8.3.6.1. Infusion/Injection-Related Reactions 76
8.4. Pharmacokinetics 77
8.5. Genetics 77
8.6. Biomarkers 77
8.7. Immunogenicity Assessments 77
8.8. Medical Resource Utilization and Health Economics 77
8.9. Storage of Blood Samples After the Study 77
9. STATISTICAL CONSIDERATIONS 78
9.1. Statistical Hypotheses 78
9.2. Analysis Sets 78
9.3. Statistical Analyses 78
9.3.1. General Considerations 78
9.3.2. Primary Endpoint(s)/Estimand(s) Analysis 79

9.3.3. Other Endpoint(s)/Estimand(s) Analysis 79
9.4. Interim Analysis 79
9.5. Sample Size Determination 80
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 81
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 81
10.1.1. Regulatory and Ethical Considerations 81
10.1.2. Financial Disclosure 81
10.1.3. Informed Consent Process 82
10.1.4. Recruitment Strategy 83
10.1.5. Data Protection 83
10.1.6. Committees Structure 83
10.1.6.1. Data Safety Monitoring Board 83
10.1.7. Dissemination of Clinical Study Data 83
10.1.8. Data Quality Assurance 84
10.1.8.1. Data Handling and Record Keeping 85
10.1.8.2. Quality Assurance Audit 85
10.1.8.3. Quality Control 85
10.1.9. Source Documents 86
10.1.10. Study and Site Start and Closure 86
10.1.11. Publication Policy 87
10.2. Appendix 2: Clinical Laboratory Tests 87
10.2.1. Other Screening Tests 89
10.2.1.1. Hepatitis B Virus 89
10.2.1.2. Hepatitis C Virus 89
10.2.1.3. Human Immunodeficiency Virus 89
10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 91
10.3.1. Definition of AE 91
10.3.2. Definition of SAE 92
10.3.3. Recording and Follow-up of AE and/or SAE 92
10.3.4. Reporting of SAEs 94

10.4. Appendix 4: Contraceptive and Barrier Guidance....95
10.4.1. Woman of Childbearing Potential....95
10.4.2. Contraception Guidance....95
10.4.2.1. Female Contraception for Women of Childbearing Potential....95
10.4.2.2. Male Contraception....96
10.5. Appendix 5: Administrative Information....97
10.6. Appendix 6: Possible Adaptations to Protocol Due to the COVID-19 Pandemic....97
10.6.1. COVID-19 Risk Assessment for Participant Safety....97
10.6.2. COVID-19 Risk Mitigation....97
10.6.3. Possible Changes in Study Design Due to the COVID-19 Pandemic....98
10.6.3.1. Implementation of This Appendix....98
10.6.3.2. Testing for COVID-19....98
10.6.3.3. Study Protocol Changes....98
10.7. Appendix 8: Country-Specific Requirements....99
10.7.1. France-specific Requirements....99
10.7.2. Germany-specific Requirements....99
11. REFERENCES....101

LIST OF TABLES

Table 1: Schedule of Activities: Part A (Study Start Through W21)....40
Table 2: Schedule of Activities: Part B (After W21 Through End of the Study)....44
Table 3: Potential Risks and Mitigation Strategies....48
Table 4: IMP Used in This Study....59
Table 5: Study Arms During the Randomized Treatment Period....59
Table 6: Analysis Sets....78
Table 7: AE Probability by Incidence Rate....80
Table 8: Protocol-Required Safety Laboratory Tests....88
Table 9: Interpretation of Hepatitis B Serological Test Results....89
Table 10: Interpretation of the Hepatitis C Antibody Test....89
Table 11: Interpretation of HIV Test Results in Combination With the Patient's Clinical Condition and CD4 Count....90

LIST OF FIGURES

Figure 1: Schema for ARGX-113-2003 Study.....38

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AChE	acetylcholinesterase inhibitors
AChR	acetylcholine receptor
AChR-Ab	anti-acetylcholine receptor antibodies
ADA	antidrug antibodies
AE	adverse event
AESI	adverse events of special interest
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	clinical study report
D1	day 1
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EoS	end of study
[redacted]	[redacted]
ET	early termination
Fc	fragment crystallizable region
FcRn	neonatal Fc receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin

Abbreviation	Definition
IgG	immunoglobulin γ
IgG1	immunoglobulin γ1
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
ITT	intention-to-treat
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
MG-ADL	Myasthenia Gravis – Activities of Daily Living
[redacted]	[redacted]
NA	not applicable
Nab	neutralizing antibody
NCI	National Cancer Institute
[redacted]	[redacted]
NSIDs	nonsteroidal immunosuppressants
PD	pharmacodynamics
PK	pharmacokinetics
PPE	personal protection equipment
q7d	every 7 days
q2w	every 2 weeks
q3w	every 3 weeks
QMG	Quantitative Myasthenia Gravis
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Systems
SFU	safety follow-up
SIB	suicide ideation and behavior
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse events

Abbreviation	Definition
TP	treatment period
[redacted]	[redacted]
VAS	visual analog scale
WOCBP	women of childbearing potential
Wn	visit of week (number)

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3b, Randomized, Open-label, Parallel-Group Study to Evaluate Different Dosing Regimens of Intravenous Efgartigimod to Maximize and Maintain Clinical Benefit in Patients With Generalized Myasthenia Gravis

Brief Title:

An open-label study to investigate the clinical efficacy of different dosing regimens of efgartigimod IV in patients with generalized myasthenia gravis

Rationale:

The aim is to compare intravenous efgartigimod (efgartigimod IV) 10 mg/kg administered in a continuous regimen with efgartigimod IV 10 mg/kg (called investigational medicinal product [IMP]) administered in a cyclic regimen in patients with generalized Myasthenia Gravis (gMG). The continuous regimen comprises an infusion every 2 weeks (q2w). The cyclic regimen comprises a treatment period (TP) of 4 once-weekly (q7d) infusions of IMP, followed by a 4-week intertreatment period (IP). Efgartigimod has been well-tolerated and has had a favorable benefit-risk assessment in clinical studies conducted to date.

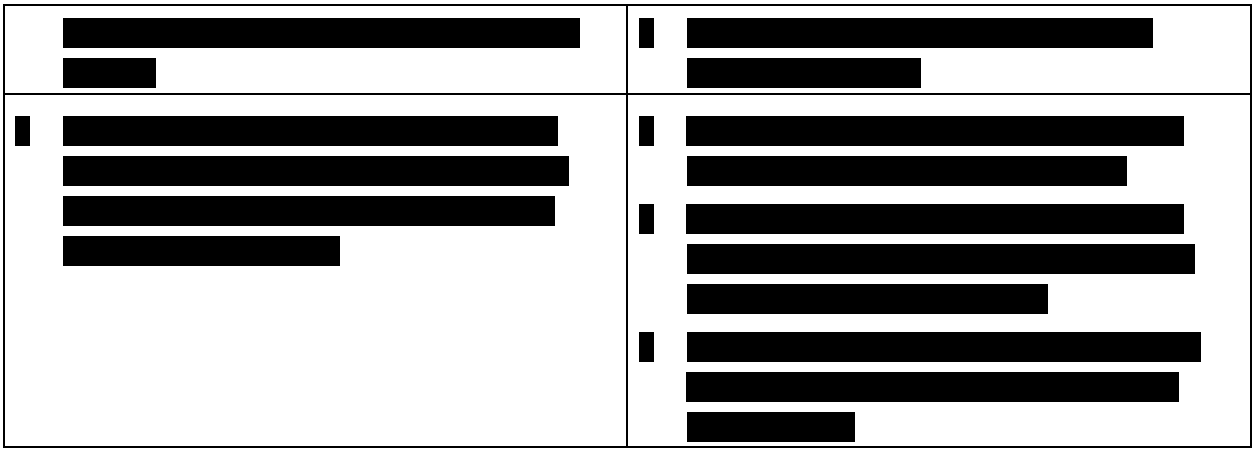
The clinical efficacy and maximum clinical effect of each regimen will be compared. The safety and tolerability of both treatment regimens will also be assessed.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the clinical efficacy of efgartigimod IV 10 mg/kg administered in a q2w continuous regimen compared to that administered in a cyclic regimen	• Mean of the average Myasthenia Gravis Activities of Daily Living (MG-ADL) total score change from baseline during the visit of week (W)1 through W21 by regimen arm
Secondary	
• To evaluate the safety and tolerability of both treatment regimens used throughout the study	• Incidence and severity of adverse events (AEs), incidence of serious adverse events (SAEs), incidence of AEs of special interest (AESIs), and changes in laboratory test results, vital sign measurements, and electrocardiogram results

• To assess the clinical efficacy of efgartigimod IV in both treatment regimens over time	• Change from baseline in the MG-ADL total score over time • Normalized area under the effect curve (AUEC) of MG-ADL total score improvement from baseline during the following intervals: o day 1 through W7 o W7 through W14 o W14 through W21 o W7 through W21 • Characterization of MG-ADL total score change from baseline during the following 5 intervals using mean and standard deviation: o W1 through W7 o W8 through W14 o W15 through W21 o W8 through W21 o W1 through W21 • Number and percentage of participants who have a ≥ 2, 3, 4, or 5 points improvement in MG-ADL total score from baseline during the following 5 intervals: o W1 through W7 o W8 through W14 o W15 through W21 o W8 through W21 o W1 through W21 • Percentage of time participants have a reduction in MG-ADL total score of at least 2 points from baseline during W4 through W21
• To compare the number of participants who achieve maximal clinical effect during different treatment regimens	• Number and percentage of participants who achieve minimal symptom expression (MSE), defined as a MG-ADL

	total score of 0 or 1, in the following 5 intervals: ○ W1 through W7 ○ W8 through W14 ○ W15 through W21 ○ W8 through W21 ○ W1 through W21
Exploratory	
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]



Overall Design:

ARGX-113-2003 is a randomized, open-label, parallel-group, multicenter phase 3b study in AChR-Ab seropositive adult patients with gMG that has been designed to evaluate the efficacy, safety, and tolerability of IMP administered using 2 dosing regimens: cyclic and continuous.

All participants will start Part A and receive efgartigimod infusions q7d during a 3-week induction period for a total of 4 infusions. After the fourth infusion at W3, participants will continue treatment with IMP in the regimen comparison period, based on the treatment regimen arm they were assigned at randomization. Participants will be randomized 3:1 to the continuous regimen arm or to the cyclic regimen arm. The cyclic regimen comprises IMP administered q7d in 3-week TPs for 4 infusions, separated by 4-week IPs. The continuous regimen comprises administration q2w continuously through W21. After W21, Part B will start, and all participants will receive efgartigimod in the continuous regimen, either q2w or q3w, depending on clinical assessment.

The first 3 infusions of the first TP will be administered at the investigative site. Subsequent doses of IMP may be administered either at the study site or using off-site infusions (if permitted by local regulations), depending on participant/site preference, regional availability of off-site infusion services, and the participant's tolerance for the infusion as determined by the investigator. Assessments shown in the Schedule of Activities (SoA) will be performed virtually if the participant does not attend a study visit at the site.

Part A

All participants will receive 4 weekly IMP infusions at day 1 (W0), W1, W2, and W3. Participants randomized to the cyclic regimen arm will receive an additional 2 cycles of efgartigimod (each including TP infusions q7d for a total of 4 infusions in 3 weeks followed by a fixed 4-weeks IP), starting at W7. Participants randomized to the continuous regimen arm will receive efgartigimod q2w, starting at W5. Part A ends after all predose assessments have been performed at the W21 visit.

Part B

Part B begins with the infusion at the W21 visit. The assessments taken at W21 will also serve as the baseline assessments for Part B. Participants in the cyclic regimen arm will receive

1 additional TP of 4 weekly infusions during W21 through week 24 as bridging doses before switching to a continuous regimen during week 26. Participants in the continuous regimen arm will continue with the continuous regimen in Part B.

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 one of these options after completing Part A of the study.

Criteria for Switching from Dosing Every 2 Weeks to Every 3 Weeks

The dose of the concomitant MG therapy should not be changed during the transition between the q2w and q3w dosing regimens. In Part B, participants will be assessed for maintenance of clinical benefit to determine if they can transition to receiving infusions q3w instead of q2w. After W21 for participants in the continuous regimen arm or during week 28 for participants in the cyclic regimen arm, participants who have maintained clinical improvement, based on clinical judgment and guided by the MG-ADL scale, will have the option to transition to receiving IMP q3w. All other participants will continue to receive IMP infusions q2w. Participants unable to maintain clinical improvement based on clinical judgment after transitioning to the q3w infusion regimen will return to the q2w infusion regimen. The decision to switch between the q2w and q3w dosing regimens must be made on the last dosing day of the current dosing regimen (ie, at least 2 weeks before the next dose).

Participants who resume the q2w regimen and maintain clinical improvement for 1 year after restarting the q2w regimen will have another opportunity to transition to the q3w regimen.

Concomitant gMG Medication

Permitted concomitant gMG treatments include:

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

Participants receiving corticosteroids and/or NSIDs must be on a stable dose for at least 1 month before screening. Concomitant gMG treatment must be administered at a stable dose and from screening through W21.

After W21, there are no restrictions on concomitant gMG therapy, and weaning off these medications is permitted.

Prohibited Medication:

The following treatments will be prohibited throughout the study:

- any monoclonal antibody
- IV or subcutaneous (SC) IgG, unless it is used as rescue therapy.
- any other experimental/study IMP
- live or live-attenuated vaccines

Any change in gMG therapy during Part A is also prohibited. There are no restrictions in part B.

Participants who receive prohibited medication will be discontinued from the study after performing an early termination (ET) visit within 7 days of the early discontinuation decision and a safety follow-up (SFU) visit 60 ± 3 days after the participant's last dose of IMP.

Participants will not be discontinued from the study in case of a protocol deviation due to the following prohibited activities:

- increasing the dose or frequency of corticosteroids
- starting a new type of steroid
- increasing the dose or frequency of a NSID
- starting a new NSID
- increasing the dose or frequency of an AChE inhibitor
- decreasing the dose or frequency of a corticosteroid, a NSID, or an AChE inhibitor

Rescue Therapy

Plasma exchange, IgG therapy, immunoadsorption, or an increase in the dosage and/or receiving a new corticosteroid are considered rescue therapy if 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 as indicated by new or worsening respiratory/bulbar symptoms or a ≥ 2-point increase in any individual nonocular item on the MG-ADL scale compared with the previous visit.

The date and time of the rescue medication, the name, dosage, and frequency of the rescue medication, and the response to the rescue therapy, as measured by the MG-ADL total score, will be recorded on the eCRF. A maximum of 3 rescue therapy treatments is allowed per year.

Participants will not be discontinued after receiving ≤ 3 rescue therapy treatments unless the investigator believes it is in the best interest of the participant.

Discontinuation From the Study

Participants must discontinue the study if:

- Participant becomes pregnant or intends to become pregnant (refer to Section 8.2.7).
- Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed).
- Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of NCI-CTCAE grade 4 that is considered related to IMP by the sponsor.
- Participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship to the IMP

- Participant receives a prohibited medication or substance (Section 6.9).
- Participant receives more than 3 rescue therapy treatments per year

If a participant needs to be discontinued from the study, they will stop receiving efgartigimod immediately and perform an ET visit within 7 days of the early discontinuation decision. Additionally, the participant will complete a SFU visit 60 ± 3 days after their last dose of efgartigimod and discontinue from the study.

A SFU visit 60± 3 days after the last dose of IMP should always occur for participants who complete the EoS visit. When a participant continues efgartigimod via commercial access or through another patient access program for gMG, this SFU visit may be done by a phone call, assessing only AEs and concomitant therapy and procedures.

Temporary Discontinuation of IMP

Participants may have a temporary discontinuation of the IMP if necessary, without being required to discontinue early from the study. Participants can temporarily discontinue the IMP because of a temporary medical condition that puts them at undue risk (ie, symptoms of infection, abnormalities in safety laboratory assessments). These participants may still be eligible for additional doses of IMP. If a dose cannot be administered within a visit window as specified in the SoA, then that dose will be missed, and the treatment interruption and the reason for the missed dose(s) will be documented. All reasonable efforts will be made to prevent missed doses. The next planned dose can be administered to the participant at the next scheduled dosing visit if the investigator determines that the undue risk has been resolved. The participant must continue to participate in all scheduled visits while the IMP is temporarily discontinued.

Continued Access to IMP:

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

Brief Summary:

The purpose of this open-label study is to investigate the efficacy, safety, and tolerability of a continuous regimen of efgartigimod compared with a cyclic regimen in participants with gMG.

Study details include:

- The study duration will be up to 138 weeks (including screening)
  - Part A (regimen comparison period) – 21 weeks
  - Part B (extension period) – up to 105 weeks
  - Safety follow-up: up to 9 weeks
- The visit frequency, including virtual visits, will be weekly through W21 and every 5 weeks for the remainder of the study.

Number of Participants:

Approximately 72 participants will be enrolled and randomized at day 1 (W0) in a 3:1 ratio to receive either continuous q2w treatment or cycles of efgartigimod during the regimen comparison period.

Note: *Enrolled* means the participant agrees to participate in the clinical study by completing the informed consent process.

Intervention Groups and Duration:

The study duration is a maximum of 138 weeks, comprising the following study periods:

- Screening period – approximately 2 weeks, with an optional additional 7 days allowed to ensure all test results have been received
- Part A (regimen comparison period) – 21 weeks
- Part B (extension period) – up to 105 weeks
- Safety follow-up: up to 9 weeks

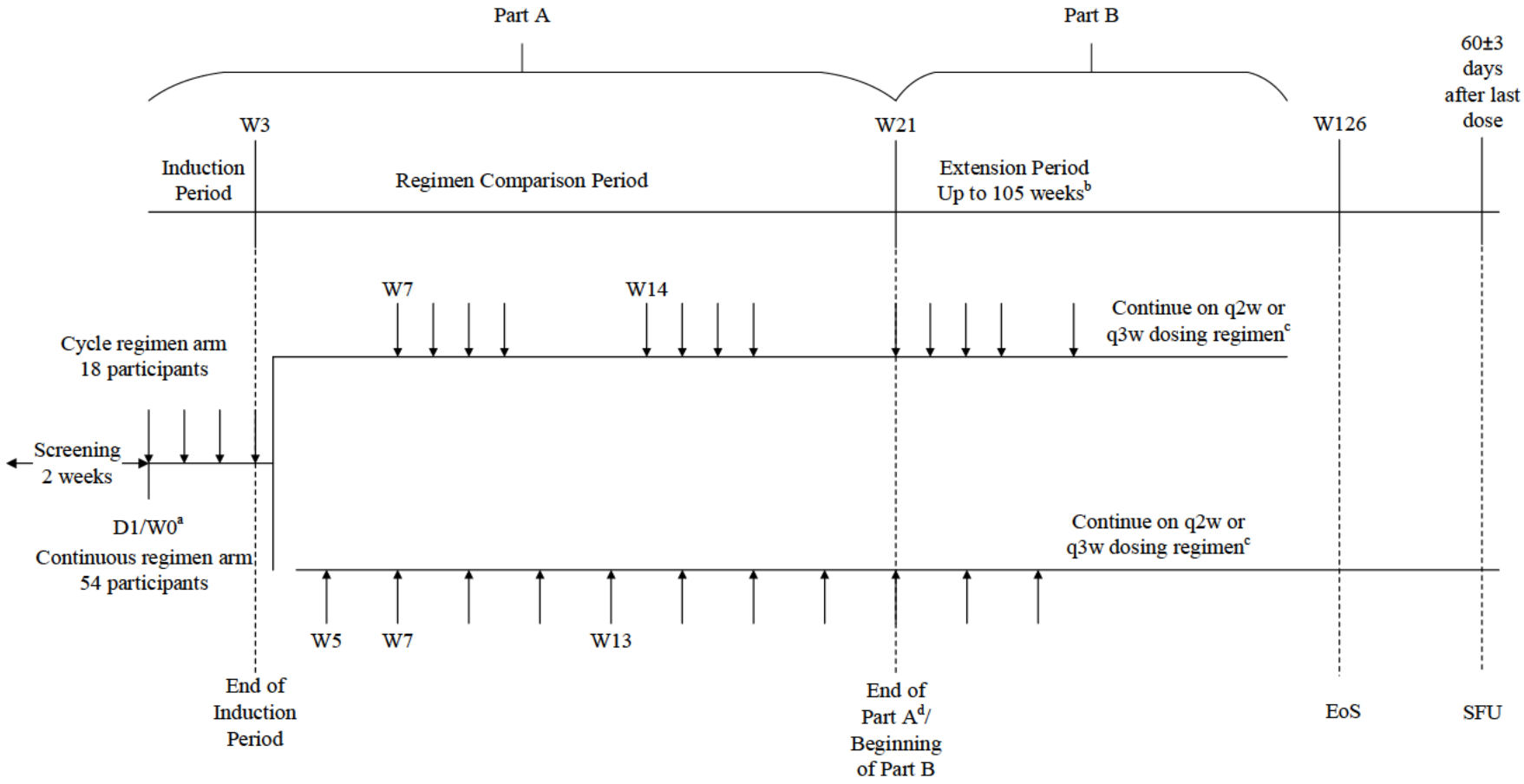
Participants will receive efgartigimod throughout the study. Starting after the W3 visit through the W21 visit, participants will be on either a cyclic regimen or a continuous regimen based on the randomization performed on day 1. In Part B, all participants will transition to a continuous regimen.

Data Monitoring/Other Committee: Yes

A DSMB has been appointed for this study. The DSMB is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for patient safety. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

1.2. Schema

Figure 1: Schema for ARGX-113-2003 Study



D1=day 1; EoS=end of study; q2w=every 2 weeks; q3w=every 3 weeks; SFU=safety follow-up; TP=treatment period; Wn=visit of week (number)
[a] At day 1, participants will be randomized 3:1 to the continuous dosing regimen arm or the cyclic regimen arm, respectively.
[b] Study duration is up to 138 weeks.

[c] Participants in the cyclic regimen arm will start part B with 1 additional TP of 3 weeks during W21 through W24 as bridging doses before switching to continuous dosing starting during W26. Participants in the continuous regimen arm will continue with the continuous dosing regimen. During part B, participants who maintain clinical improvement receiving the q2w dosing regimen can switch to the q3w dosing regimen. Participants in part B who do not maintain clinical improvement on the q3w dosing regimen will be able to switch back to the q2w dosing regimen.

[d] 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 completing part A of the study. If participants continue receiving efgartigimod through either of these other means instead of continuing to part B, they will not receive the scheduled dose at W21 and no SFU will be performed. If participants do not continue to part B and will not continue receiving IMP through these other means, they may receive the scheduled dose at W21 and a SFU visit will be performed after 60 (± 3) days.

1.3. Schedule of Activities

Table 1: Schedule of Activities: Part A (Study Start Through W21)

	Screening	Induction Period			Regimen Comparison Period											ET[a]	SFU[a]	UNS[b]
		D1 (W0)	W1 W2	W3	W4	W5 W6	W7	W8 W9 W10	W11	W12 W13	W14	W15 W16 W17	W18	W19 W20	End of Part A (W21)			
Study Day (± days)	**-14 to -1**	**1**	**8 15 (±2)**	**22 (±2)**	**29 (±2)**	**36 43 (±2)**	**50 (±2)**	**57 64 71 (±2)**	**78 (±2)**	**85 92 (±2)**	**99 (±2)**	**106 113 120 (±2)**	**127 (±2)**	**134 141 (±2)**	**148 (±2)**	**NA**	**NA**	**NA**
Required on-site visits[c]	**X**	**X**	**X**		**X**		**X**				**X**				**X**	**X**	**X**	
Informed consent[d]	X																	
Eligibility criteria	X	X																
Demographic characteristics	X																	
Medical and surgical history	X																	
Pregnancy test (WOCBP only)[e]	X	X			X		X				X				X	X	X	X
Viral screening[f]	X																	
SARS-CoV-2 test[g]	X														X[h]			X
Randomization		X																
Height and weight[i]	X	X			X		X				X				X	X		X
MG-ADL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]																		

	Screening	Induction Period			Regimen Comparison Period										ET[a]	SFU[a]	UNS[b]
		D1 (W0)	W1 W2	W3	W4	W5 W6	W7	W8 W9 W10	W11	W12 W13	W14	W15 W16 W17	W18	W19 W20	End of Part A (W21)			
Study Day (± days)	**-14 to -1**	**1**	**8 15 (±2)**	**22 (±2)**	**29 (±2)**	**36 43 (±2)**	**50 (±2)**	**57 64 71 (±2)**	**78 (±2)**	**85 92 (±2)**	**99 (±2)**	**106 113 120 (±2)**	**127 (±2)**	**134 141 (±2)**	**148 (±2)**	**NA**	**NA**	**NA**
Required on-site visits[c]	**X**	**X**	**X**		**X**		**X**				**X**				**X**	**X**	**X**	
[redacted]																		
SIB risk monitoring[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X				X				X	X	X	X
Vital signs	X	X			X		X				X				X	X	X	X
ECG	X	X			X		X				X				X	X	X	X
Blood sampling[l]																		
Clinical safety laboratory tests[m]	X	X			X		X				X				X	X	X	X
[redacted]																		
Urinalysis	X	X			X		X				X				X	X	X	X

	Screening	Induction Period			Regimen Comparison Period											ET[a]	SFU[a]	UNS[b]
		D1 (W0)	W1 W2	W3	W4	W5 W6	W7	W8 W9 W10	W11	W12 W13	W14	W15 W16 W17	W18	W19 W20	End of Part A (W21)			
Study Day (± days)	**-14 to -1**	**1**	**8 15 (±2)**	**22 (±2)**	**29 (±2)**	**36 43 (±2)**	**50 (±2)**	**57 64 71 (±2)**	**78 (±2)**	**85 92 (±2)**	**99 (±2)**	**106 113 120 (±2)**	**127 (±2)**	**134 141 (±2)**	**148 (±2)**	**NA**	**NA**	**NA**
Required on-site visits[c]	**X**	**X**	**X**		**X**		**X**				**X**				**X**	**X**	**X**	
IMP administration[q]		X	X	X	Based on treatment regimen[r]										X[s]			
Prior/concomitant therapy and procedures[t]	Continuous monitoring																	
Adverse events[t]	Continuous monitoring																	

AChR-Ab=anti-acetylcholine receptor antibody; ADA=antidrug antibodies; AE=adverse event; ECG=electrocardiogram; [redacted]; EoS=end of study; ET=early termination; gMG=generalized myasthenia gravis; ICF=informed consent form; IgG=immunoglobulin γ; IMP=investigational medicinal product; IV=intravenous; MG-ADL=Myasthenia Gravis Activities of Daily Living; [redacted] NA=not applicable; Nab=neutralizing antibodies; [redacted]; PD=pharmacodynamics; PHQ-9=9-item Patient Health Questionnaire; PK=pharmacokinetic; q2w=every 2 weeks; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SFU=safety follow-up; SIB=suicide ideation and behavior; SoA=schedule of activities; [redacted] for Medication – 9 items; UNS=unscheduled; WOCBP=women of childbearing potential; Wn=visit of week (number)

Note: At visits when the participant receives efgartigimod, all scheduled activities will be performed before the start of the infusion except for the postdose PK blood sample.

Note: Part A ends after all predose assessments have been performed at W21. Part B begins with the infusion at W21.

[a] Any participant who discontinues the study will immediately stop receiving efgartigimod and should attend an ET visit 7 (± 3) days after the early discontinuation decision and a SFU visit 60 (± 3) days, after their last dose of efgartigimod. An SFU visit 60 ± 3 days after the last dose of IMP should always occur for participants who complete the EoS visit. When a participant continues efgartigimod via commercial access or through another patient access program for gMG, this SFU visit may be done by a phone call, assessing only AEs and concomitant therapy and procedures.

[b] A UNS visit may occur at the request of the participant or the investigator. During the UNS visit, activities listed in the SoA may be performed at the investigator's discretion. Depending on the reason that prompted the visit, the UNS visit may be virtual if feasible.

[c] These indicated visits must occur at the study site. All other infusion visits (W3, W5, W8-W11, W13, W15-W17, and W19) may occur off-site (if permitted by local regulations, see Section 10.7 for country-specific requirements) or at the study site, depending on the participant's preference and regional availability of off-site infusion services. All other visits may be performed virtually.
[d] No study-related activities will be initiated before the participant signs the ICF.
[e] Pregnancy testing will be a highly sensitive serum test at screening, and a urine test at all subsequent visits. Local regulations will be followed if they require more stringent or frequent testing. See Section 8.2.7.
[f] The virology screen tests for those infections described in exclusion criteria 8. See Section 10.2.1.
[g] Additional tests may be performed as needed based on local regulations. See Section 8.2.6.4.
[h] Participants who enter part B will have a SARS-CoV-2 test if the COVID-19 pandemic is ongoing where the participant resides.
[i] Height will be measured at screening only.
[j] The baseline assessment refers to background medication administered for gMG.
[k] The SIB risk monitoring assessment is based on question 9 of the PHQ-9.
[l] At dosing visits, all blood samples will be taken predose unless otherwise specified.
[m] Blood samples for clinical laboratory safety assessments will be taken while the participant is in the fasted condition. See Section 8.2.6.1..
[n] ADA samples will be stored for potential testing of Nab against efgartigimod if PK/PD results are inconclusive. See Section 8.2.8.
[o] The PD analysis comprises total IgG and AChR-Ab levels. See Section 8.1.1.
[p] On dosing days, PK samples will be collected both predose (within 1 hour before the start of infusion) and at the end of the infusion (within 1 hour after the end of infusion). On nondosing days, 1 PK sample will be collected.
[q] Efgartigimod IV infusions will be administered either at the site or off-site by a home nurse as indicated by the visits schedule (see Section 10.7 for country-specific requirements). The home nurse's tasks at an off-site visit may be performed by another qualified person (see Section 6.2.1). Participants will be monitored for at least 30 minutes (see Section 10.7 for country-specific requirements) after the end of the infusion. Off-site administrations will be permitted based on the investigator's judgment. There should be at least 3 IMP administrations received by the patient on-site before decision to start with off-site administration will be taken by the investigator.
[r] Participants randomized to the cyclic regimen arm will receive weekly infusions of IMP on W7-W10, and W14-W17. Participants randomized to the continuous treatment arm will receive IMP q2w from W5-W21.
[s] The infusion at W21 is the first activity of part B. The infusion is only performed if the participant is eligible to enter part B.
[t] Adverse events, use of concomitant therapies, use of rescue therapy, vaccinations received, and medical procedures performed on the participants will be collected from the time the ICF is signed until the last study-related activity. All available vaccination history should be recorded as part of the participant's prior medication for vaccinations received in the past, or as concomitant medication for vaccines received during the study. Vaccination history and relevant prior therapy will be collected at screening.

Table 2: Schedule of Activities: Part B (After W21 Through End of the Study)

Visit Type	**Abridged Visit**[a]	**On-site Visit**	**End of Study**	**Early Termination**	**Safety Follow-Up**	**Unscheduled**
	AVn	**OVn**	**EoS**[b]	**ET**[c]	**SFU**[c]	**UNS**[d]
Study Week	**26, 31, 41, 46, 56, 61, 71, 76, 86, 91, 101, 106, 116, 121**	**36, 51, 66, 81, 96, 111**	**126**	**NA**	**NA**	**NA**
Study Day (± days)	**183, 218, 288, 323, 393, 428, 498, 533, 603, 638, 708, 743, 813, 848 (±3)**	**253, 358, 463, 568, 673, 778 (±3)**	**833 (±3)**	**NA**	**NA**	**NA**
Required on-site visits[e]		**X**	**X**	**X**	**X**	
Weight		X	X	X		X
MG-ADL	X	X	X	X		X
[redacted]						
SIB risk monitoring[f]	X	X	X	X	X	X
Physical examination		X	X	X	X	X
Vital signs		X	X	X	X	X
ECG		X	X	X	X	X
Blood Sampling[g]						
Clinical laboratory tests[h]		X	X	X	X	X
[redacted]						

Visit Type	Abridged Visit[a]	On-site Visit	End of Study	Early Termination	Safety Follow-Up	Unscheduled
	AVn	OVn	EoS[b]	ET[c]	SFU[c]	UNS[d]
Study Week	**26, 31, 41, 46, 56, 61, 71, 76, 86, 91, 101, 106, 116, 121**	**36, 51, 66, 81, 96, 111**	**126**	**NA**	**NA**	**NA**
Study Day (± days)	**183, 218, 288, 323, 393, 428, 498, 533, 603, 638, 708, 743, 813, 848 (±3)**	**253, 358, 463, 568, 673, 778 (±3)**	**833 (±3)**	**NA**	**NA**	**NA**
Required on-site visits[e]		**X**	**X**	**X**	**X**	
Urinalysis		X	X	X	X	X
Urine pregnancy test (WOCBP only)[l]		X	X	X	X	X
SARS-CoV-2 test[m]						X
IMP administration[n]	Based on treatment regimen[o]					
Concomitant therapy and procedures[p]	Continuous monitoring					
Adverse events[p]	Continuous monitoring					

AChR-Ab=anti-acetylcholine receptor antibody; ADA=antidrug antibodies; AE=adverse event; AVn=abridged visit (number); EoS=end of study; [redacted]; ET=early termination; IgG=immunoglobulin γ; IMP=investigational medicinal product; IV=intravenous; MG-ADL=Myasthenia Gravis – Activities of Daily Living; [redacted] NA=not applicable; Nab=neutralizing antibodies; [redacted] OVn=on-site visit (number); PD=pharmacodynamics; PHQ-9=9-item Patient Health Questionnaire; PK=pharmacokinetic; q2w=every 2 weeks; q3w=every 3 weeks; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SFU=safety follow-up; SIB=suicide ideation and behavior; SoA=schedule of activities; TP=treatment period; [redacted]; UNS=unscheduled; WOCBP=women of childbearing potential; Wn=visit of week (number)

Note: At visits when the participant receives efgartigimod, all scheduled activities will be performed before the start of the infusion except for the postdose PK blood sample.

Note: Part B begins with the infusion at W21. Refer to for the "IMP administration" row under the W21 column in Table 1 for this activity.

[a] Abridged visits are visits that can be performed virtually or at the study site.

[b] At the end of the study, argenx will comply with all local regulations for ensuring continued access to IMP medically identified as essential.

[c] Any participant who discontinues the study will immediately stop receiving efgartigimod and should attend an ET visit 7 (± 3) days after the early discontinuation decision and a SFU visit 60 (± 3) days, after their last dose of efgartigimod. A SFU visit 60 ± 3 days after the last dose of IMP should always

occur for participants who complete the EoS visit. When a participant continues efgartigimod via commercial access or through another patient access program for gMG, this SFU visit may be done by a phone call, assessing only AEs and concomitant therapy and procedures.

[d] A UNS visit may occur at the request of the participant or the investigator. During the UNS visit, activities listed in the SoA may be performed at the investigator's discretion. Depending on the reason that prompted the visit, the UNS visit may be virtual if feasible.

[e] These indicated visits must occur at the study site. All other infusion visits may occur off-site (if permitted by local regulations, see Section 10.7 for country-specific requirements) or at the study site, depending on the participant's preference and regional availability of off-site services. All other visits may be performed virtually.

[f] The SIB risk monitoring assessment is based on question 9 of the PHQ-9.

[g] At dosing visits, all blood samples will be taken predose unless otherwise specified.

[h] Blood samples for clinical laboratory safety assessments will be taken while the participant is in the fasted condition. See Section 8.2.6.1.

[i] ADA samples will be stored for potential testing of Nab against efgartigimod if PK/PD results are inconclusive. See Section 8.2.8.

[j] The PD analysis comprises total IgG and AChR-Ab levels. See Section 8.1.1.

[k] On dosing days, PK samples will be collected both predose (within 1 hour before the start of infusion) and at the end of the infusion (within 1 hour after the end of infusion). On nondosing days, 1 PK sample will be collected.

[l] Local regulations will be followed if they require more stringent or frequent pregnancy testing.

[m] Additional tests may be performed as needed based on local regulations. See Section 8.2.6.4.

[n] Efgartigimod IV infusions will be administered either at the site or off-site by a home nurse at the indicated visits (see Section 10.7 for country-specific requirements). The home nurse's tasks at an off-site visit may be performed by another qualified person (see Section 6.2.1). Participants will be monitored by the study staff for at least 30 minutes (see Section 10.7 for country-specific requirements) after the end of the infusion. Off-site administrations will be permitted based on the investigator's judgment. There should be at least 3 IMP administrations received by the participant on-site before decision to start with off-site administration will be taken by the investigator.

[o] Participants will either be on the q2w or q3w treatment regimen, based on clinical judgment. Participants who were randomized to the cyclic dosing regimen will receive 1 more TP starting on W21, followed by a transition to a continuous dosing regimen starting at W26. Participants may switch to the q3w dosing regimen, based on clinical judgment and guided by the MG-ADL scale. If participants on the q3w dosing regimen do not maintain clinical effect, they will switch back to the q2w dosing regimen, with another opportunity to switch to the q3w dosing regimen in 1 year.

[p] Adverse events, use of concomitant therapies, use of rescue therapy, vaccinations received, and medical procedures performed on the participants will be collected from the time the informed consent form is signed until the last study-related activity. Vaccinations received during the study should be recorded as concomitant medication.

2. INTRODUCTION

Efgartigimod, a human immunoglobulin (Ig) γ1 (IgG1)-derived Fc fragment that binds with nanomolar affinity to human FcRn, is being developed for the treatment of generalized myasthenia gravis (gMG).

2.1. Study Rationale

The aim is to compare a continuous regimen of intravenous efgartigimod (efgartigimod IV) 10 mg/kg to the cyclic regimen in patients with gMG. When receiving a continuous regimen, participants will receive an infusion of efgartigimod IV 10 mg/kg (called investigational medicinal product [IMP]) every 2 weeks (q2w). A cyclic regimen comprises a treatment period (TP) of 4 once-weekly (q7d) infusions of IMP, followed by a 4-week intertreatment period (IP). Efgartigimod has been well-tolerated and has had a favorable benefit-risk assessment in clinical studies conducted to date.

A continuous q2w regimen will be compared with the cyclic regimen by assessing the clinical efficacy and the maximum clinical effect. The safety and tolerability of both treatment regimens will also be assessed.

2.2. Background

gMG is a rare, chronic, neuromuscular autoimmune disease caused by pathogenic IgGs targeting the neuromuscular junction, 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 a 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 autoantibodies are against the acetylcholine receptor (AchR).[3] Efgartigimod leads to degradation of circulating diseases-causing pathogenic antibodies by blocking FcRn.

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

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

In the phase 3 study ARGX-113-1704 in patients with gMG, treatment with efgartigimod IV 10 mg/kg resulted in a statistically significant increase in the percentage of participants responding to treatment based on the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score and the Quantitative Myasthenia Gravis (QMG) score as compared to placebo. Additionally, efgartigimod IV treatment resulted in a substantial mean percent decrease in total IgG levels as compared to no observable change in participants who received placebo, which further supported the results of the phase 2 study ARGX-113-1602. An interim analysis of the ongoing open-label extension study ARGX-113-1705 showed that the efficacy and the reduction in total IgG levels were maintained over multiple treatment cycles. In ongoing clinical studies for other autoimmune diseases (eg, primary immune thrombocytopenia, pemphigus), efgartigimod IV has been used on a continuous dosing schedule, where participants received efgartigimod IV 10 mg/kg weekly or every 2 weeks with no treatment-free period. This dosing regimen is being used to achieve an extended IgG reduction and has not yet been associated with any significant increase in risk when compared with the cyclic regimen.

Refer to the IB for more detailed information.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Overall, available data confirm that efgartigimod 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
Study Intervention		
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing infection risk.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (see Section 5.2). Infections are considered AESIs (see Section 8.3.5). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.2)
Infusion/injection-related reactions	All therapeutic proteins have the potential to elicit immune responses, potentially resulting	Monitor participants during administration and for 30 minutes (see Section 10.7 for

	in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions.	country-specific requirements) thereafter for clinical signs and symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.3.6). If an infusion reaction occurs, interrupt the infusion and implement appropriate supportive measures. Once resolved, the infusion can be resumed, and at a slower rate if necessary.

2.3.2. Overall Benefit/Risk Conclusion

Accounting for the measures taken to minimize risk to study participants, the favorable safety profile of efgartigimod, and the reported clinical benefits for patients with gMG, the potential risks identified in association with the IMP are justified by the anticipated benefits that may be afforded to participants with gMG.

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary	
• To assess the clinical efficacy of efgartigimod IV 10 mg/kg administered in a q2w continuous regimen compared to that administered in a cyclic regimen	• Mean of the average MG-ADL total score change from baseline during the visit of week (W)1 through W21 by regimen arm
Secondary	
• To evaluate the safety and tolerability of both treatment regimens used throughout the study	• Incidence and severity of AEs, incidence of serious adverse events (SAEs), incidence of AESIs, and changes in laboratory test results, vital sign measurements, and electrocardiogram results

• To assess the clinical efficacy of efgartigimod IV in both treatment regimens over time	• Change from baseline in the MG-ADL total score over time • Normalized area under the effect curve (AUEC) of MG-ADL total score improvement from baseline during the following intervals: o day 1 through W7 o W7 through W14 o W14 through W21 o W7 through W21 • Characterization of MG-ADL total score change from baseline during the following 5 intervals using mean and standard deviation: o W1 through W7 o W8 through W14 o W15 through W21 o W8 through W21 o W1 through W21 • Number and percentage of participants who have a ≥ 2, 3, 4, or 5 points improvement in MG-ADL total score from baseline during the following 5 intervals: o W1 through W7 o W8 through W14 o W15 through W21 o W8 through W21 o W1 through W21 • Percentage of time participants have a reduction in MG-ADL total score of at least 2 points from baseline during W4 through W21
• To compare the number of participants who achieve maximal clinical effect during different treatment regimens	• Number and percentage of participants who achieve minimal symptom expression (MSE), defined as a MG-ADL total score of 0 or 1, in the following 5 intervals:

	○ W1 through W7 ○ W8 through W14 ○ W15 through W21 ○ W8 through W21 ○ W1 through W21
Exploratory	
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

• [redacted]	[redacted]

Primary estimand/coprimary estimands

- Population: intention-to-treat (ITT) analysis set (see Table 6)
- Variable: mean of the average MG-ADL total score improvement during W1 through W21
- Main intercurrent events
  - Early treatment discontinuation for any reason before W21
  - Initiation of Ig therapy as rescue therapy before W21

See Section 9.3.2.

4. STUDY DESIGN

4.1. Overall Design

- This is a phase 3b, multicenter, randomized, open-label, parallel-group study to evaluate alternative dosing regimens for the IMP in patients with gMG. The clinical efficacy, maximum clinical effect, safety, and tolerability will be assessed for 2 treatment regimens: cyclic and continuous.
- The target population is adult patients with gMG who have an MG-ADL total score of ≥ 5 points and more than 50% of the total score attributed to nonocular symptoms at screening and baseline.
- All participants will be confirmed to be seropositive for AChR-Abs. During the screening or rescreening period, any historical results for AChR-Ab can be used, as long as the results are ≤ 1 year old.
- Participants must be receiving concomitant gMG treatment from screening through the end of part A (see Section 6.9).
- All participants will start part A by receiving the cyclic regimen, receiving efgartigimod infusions q7d during a 3-week induction period for a total of 4 infusions.
- After the fourth infusion at W3, the 2 regimens will be compared in a regimen comparison period. On the day 1 visit, participants will be randomized 3:1 to either the continuous or cyclic regimen. Part A ends after all predose assessments are performed at the W21 visit.
- The cyclic regimen comprises IMP administered q7d in 3-week TPs for 4 infusions, separated by 4-week Ips. The continuous regimen comprises infusions q2w.
- Part B begins with the infusion at the W21 visit, with the assessments at this visit acting as the baseline for part B. Participants in the cyclic regimen arm will receive 1 additional TP of 4 weekly infusions during W21 through W24 as bridging doses before switching to a continuous regimen at W26. Participants in the continuous regimen arm will continue with the continuous regimen in part B.
- 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 completing part A of the study.
- After W21 for participants in the continuous regimen arm or during W28 for participants in the cyclic regimen arm, participants who have maintained clinical improvement, based on clinical judgment and guided by the MG-ADL scale, will have the option to transition to receiving the IMP q3w. All other participants will continue to receive IMP infusions q2w.
- Participants who are unable to maintain clinical improvement based on clinical judgment after transitioning to the q3w infusion regimen will return to the q2w infusion regimen. The decision to switch between the q2w and q3w dosing regimens

must be made on the last dosing day of the current dosing regimen (ie, at least 2 weeks before the next dose).

- Participants who resume the q2w regimen and maintain clinical improvement for 1 year after restarting the q2w regimen will have another opportunity to transition to the q3w regimen.
- The total study duration is up to 138 weeks. The study consists of:
  - Approximately 2 weeks of screening, with an additional 7 days allowed as needed to ensure all lab tests results have been received
  - Part A (regimen comparison period) – 21 weeks
  - Part B (extension period) – up to 105 weeks
  - Safety follow-up: up to 9 weeks

4.2. Scientific Rationale for Study Design

The primary objective of this study is to assess the effect of different dosing regimens of IMP on clinical efficacy. To measure the clinical efficacy, this study uses the MG-ADL total score, a well-established measure of assessing the severity of gMG symptoms. Any impact on the QoL of the participants will be measured using the [redacted] fatigue assessments, which are standardized assessments for QoL related to gMG symptoms, generic health status, and feelings of tiredness to exhaustion, respectively. The [redacted] will be used to assess treatment satisfaction. All of these metrics focus on changes in disease symptoms and how those changes affect the participant's well-being and ability to perform daily activities.

As the efficacy of the IMP was demonstrated in a placebo-controlled study (ARGX-113-1704) and this study is designed to explore the effect of different dosing regimens on clinical efficacy, a double-blind study design is not necessary and would cause an undue burden on the participants.

4.3. Justification for Dose

The dosage of IMP has been used in previous clinical studies, including a phase 3 placebo-controlled study and an open-label extension study in participants with gMG (ARGX-113-1704 and ARGX-113-1705, respectively). Administration of efgartigimod achieved near-maximal total IgG reduction, resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in participants with gMG. Furthermore, the dose of 10 mg/kg IV has been well-tolerated and has had a favorable risk-benefit profile in clinical studies conducted to date. In ongoing clinical studies in other indications in which IMP is being administered weekly or q2w (ARGX-113-1801, ARGX-113-1803, ARGX-113-1701), no SAEs were reported as related to efgartigimod by the investigator.

4.4. End of Study Definition

The end of the study is defined as the last participant's last visit. A participant is considered to have completed the study if all periods of the study, including the EoS and SFU visits, have been completed (refer to Section 1.3).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants can be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2. At least 18 years of age, at the time of signing the informed consent

3.1. Diagnosed with gMG with confirmed documentation and supported by a physical exam and confirmed seropositivity for AChR-Abs by the central laboratory. During the screening or rescreening period, any historical results for AChR-Ab can be used, as long as the results are ≤ 1 year old.

4.1 Meets the clinical criteria as defined by the Myasthenia Gravis Foundation of America (MGFA) class II, III, or IV

5. Has an MG-ADL total score ≥ 5 at screening and the day 1 visit, with more than 50% of the score due to nonocular symptoms
6. Concomitant gMG treatment is permitted. Permitted concomitant gMG treatment includes nonsteroidal immunosuppressive drugs (NSIDs), steroids, and/or AChE inhibitors. If receiving corticosteroids and/or NSIDs, must be on a stable dose for at least 1 month before screening.

7.1 Agrees to use contraceptive measures consistent with local regulations and the following:

   a. Male participants (contraceptive measures provided in Section 10.4.2.2, refer to Section 10.7 for country-specific requirements)
   b. WOCBP (defined in Section 10.4.1) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before receiving IMP (Section 10.4.2.1, see Section 10.7 for country-specific requirements)

5.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

1.1. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection at screening that is not sufficiently resolved in the investigator's opinion

2. A positive test for SARS-CoV-2 at screening
3. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of the clinical symptoms of gMG and/or put the participant at undue risk

4. History of malignancy unless deemed cured by adequate treatment with no evidence of reoccurrence for ≥ 3 years before the first administration of the IMP. Participants with the following cancers can be included at any time, provided they are adequately treated at screening:
    a. Basal cell or squamous cell skin cancer
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)
3. Clinical evidence of other significant serious diseases, a recent (< 3 months) major surgery, or any other condition that, in the opinion of the investigator, could confound the results of the study or put the participant at undue risk
4. A thymectomy within 3 months of screening
5. Pregnant or lactating females and those who intend to become pregnant during the study or within 90 days of the last dose of IMP
6. Use of the following prior or concomitant therapies:
    a. IVIg or subcutaneous (SC)Ig within 14 days of day 1
    b. Rituximab within 6 months of day 1
    c. Eculizumab within 1 month of day 1
    d. Other monoclonal antibodies (eg, adalimumab, tocilizumab, ixekizumab) within 5 half-lives of the monoclonal antibodies before day 1
    e. Use of any other investigational product within 3 months or 5 half-lives, whichever is longer, before day 1
    f. Receipt of a live or live-attenuated vaccine within 4 weeks of screening. The receipt of any inactivated, subunit, polysaccharide, conjugate vaccine at any time before screening is not considered exclusionary.
7. Previous participation in a clinical study or patient access program during which they were treated with efgartigimod
8. Positive serum test at screening for an active viral infection with any of the following conditions (see Section 10.2.1):
    a. Hepatitis B virus (HBV) that is indictive of an acute or chronic infection (Table 9)[5]
    b. Hepatitis C virus (HCV) based on HCV antibody assay (unless associated with a negative HCV RNA test) (Table 10)
    c. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count ≤ 200 cells/mm^3 (Table 11)
9. Total IgG < 6 g/L at screening
10. Known hypersensitivity reaction to efgartigimod or any of its excipients
11. The participant stands in any relationship of dependency with the sponsor.
12. The participant has been institutionalized due to an official or judicial order.

5.3. Lifestyle Considerations

Participants will need to be fasted for each on-site visit at which safety laboratory assessments will be taken.

5.4. Screen Failures

A screen failure occurs when a participant who has signed the ICF is not assigned to IMP. A minimal set of screen failure information (demography, screen failure details, eligibility criteria, and SAE reports) is required to ensure transparent reporting of screen failure participants and address regulatory authority queries.

Individuals who do not meet the criteria for the participation in this study may be rescreened (ie, redoing the full assessments as per the SoA in Table 1) or retested (ie, redoing only some of the screening assessments) once after the sponsor's written approval.

An example of conditions under which rescreening may be considered include individuals who require treatment for an acute illness (eg, infection). These individuals may be rescreened once the illness is resolved or the medical problem is stabilized.

An example of conditions under which retesting may be considered include individuals who have clinical laboratory test values meeting 1 or more exclusion criteria that are not in line with the medical history or clinical evaluation of the individual. These individuals may be retested to confirm the value of the test(s), if still within the screening period. If it is not feasible to retest during the screening period, the individual should be rescreened.

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

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Delaying the administration of the IMP must occur if it is deemed in the best interest of the participant because of a temporary medical condition that puts him or her at undue risk. If the IMP cannot be administered within the specified time window, then that dose of the IMP must be missed (see Section 7.1.2).

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

All IMP is manufactured according to Good Manufacturing Practice regulations.

6.1. Study Intervention(s) Administered

Table 4: IMP Used in This Study

IMP label	Efgartigimod IV
IMP name	Efgartigimod formulation for IV administration
IMP description	IV, concentrate for solution for infusion for dosing of 10 mg/kg
Type	Biologic
Dose formulation	Infusion
Unit dose strength	20 mg/mL
Dosage level	10 mg/kg q2w, q3w, or q7d for 4 infusions in a TP
Route of administration	IV infusion
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by sponsor
Packaging and labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as per country requirements. The IMP will be labeled and packed in secondary containers in accordance with local laws and regulatory requirements.

Table 5: Study Arms During the Randomized Treatment Period

	Continuous Regimen	Cyclic Regimen
Arm type	Experimental	Experimental
Arm description	efgartigimod 10 mg/kg q2w	efgartigimod 10 mg/kg q7d for a total of 4 infusions per TP for 2 TPs with a fixed 4-week intertreatment period between each TP
Associated intervention labels	Efgartigimod IV	Efgartigimod IV

6.2. Preparation, Handling, Storage, and Accountability

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

6.2.1. Preparation

Efgartigimod for IV administration will be provided as a sterile, colorless, clear concentrate in glass vials. Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared

by the site staff or the home nurse before administration. The home nurse, who will go to the participant for off-site visits, can be another person qualified to perform all tasks (eg, a trained qualified physician), if applicable per local 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 the site staff or the off-site infusion vendor staff.

6.2.3. Storage

The IMP will be supplied to the pharmacy (or substitute) at the designated investigational site by and under the responsibility of the sponsor's designated IMP supply vendor.

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 temperatures or shaken, and it should be protected from direct sunlight during storage at the clinical site.

The investigator or their designee is responsible for the correct and safe storage of the IMP assigned to the clinical site, in a locked secure storage facility maintained within the appropriate temperature ranges, with access limited to those individuals authorized to dispense IMP.

6.2.4. Accountability

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

6.3. Assignment to IMP

Participants will be assigned a unique patient identification number at screening. Upon randomization, the participant will be assigned to a treatment arm according to the randomization schedule generated before the start of the study.

6.4. Measures to Minimize Bias: Randomization and Blinding

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

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of IMP and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants are dosed using off-site infusion, the dose of study intervention will be administered by a trained staff member of the designated off-site infusion service provider. The dose of the study intervention and participant identification will be confirmed at the time of dosing by the person administering the study intervention. Compliance will be assessed during virtual visits with the study site staff. Deviations from the prescribed dosage regimen should be recorded.

The investigator should promote treatment compliance by stating that compliance is necessary for the participant's safety and the validity of the study. The prescribed dose, timing, and mode of administration cannot be changed. All dates, start and end times of IMP administration, and any deviations from the intended regimen must be recorded on the electronic case report form (eCRF).

A sponsor's designated contract research organization (CRO) monitor will review the pharmacy records at each site including the drug accountability and dispensing records on which the pharmacist or designated person should record all IMP released for participant use. The sponsor's designated CRO monitor will compare the dispensing record and vials with the individual participant's identifiers, kit number, and visit schedule to confirm that the participant received the correct treatment and dose, and that the dosing schedule is correct.

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

6.5.1. Handling Missed Doses of the IMP

All efforts will be made to ensure the participant receives all administrations of IMP on the scheduled day. If a participant misses any scheduled doses, they will not be discontinued from the study (Section 7).

6.5.2. Protocol Deviations

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

6.6. Dose Modification

The maximum total efgartigimod dose per efgartigimod infusion is 1200 mg for participants weighing ≥ 120 kg. The IMP weight-based dose will be recalculated if a participant's weight has changed by more than or equal to 10% from baseline.

The dose of the concomitant gMG therapy should not be changed during the transition between the q2w and q3w dosing regimens. In part B, participants will be assessed for the maintenance of

clinical benefit to determine if they can transition to receiving infusions q3w instead of q2w. After W21 for participants in the continuous regimen arm or after W28 for participants in the cyclic regimen arm, participants who have maintained clinical improvement, based on clinical judgment and guided by the MG-ADL scale, will have the option to transition to receiving IMP q3w. All other participants will continue to receive IMP infusions q2w. Participants who are unable to maintain clinical improvement based on the clinical judgment after transitioning to the q3w infusion regimen will return to the q2w infusion regimen. The decision to switch between q2w and q3w dosing regimens must be made on the last dosing day of the current dosing regimen (ie, at least 2 weeks before the next dose).

Participants who resume the q2w regimen and maintain clinical improvement for 1 year after restarting the q2w regimen will have another opportunity to transition to the q3w regimen.

6.7. Continued Access to Study Intervention 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.

6.8. Treatment of Overdose

Any dose of efgartigimod greater than 10% of the planned dosage amount (see Section 1.3) will be considered an overdose. Furthermore, there must be at least 3 days between 2 consecutive doses.

The sponsor does not recommend specific treatment for an overdose.

If an overdose occurs, the investigator will:

- Evaluate the participant to determine if IMP will be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate and at least until the next scheduled follow-up).
- Immediately report the overdose, the quantity of the excess dose, and the overdose duration to the sponsor.

6.9. Concomitant Therapy

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

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

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

6.9.1. Prior Medications and Procedures

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

Clinically relevant prior medications and procedures include:

- Prior gMG medications and procedures received within 1 year before screening, including the participant's response to the therapy and the reason for changing medication and dose
- Prior non-gMG medications and procedures received within 6 months before screening
- All available vaccination history. Any vaccination information that the participant, their caregiver, or their legally authorized representative can remember should be recorded on the eCRF with the brand name of the vaccine and the date of vaccination, if possible.

6.9.2. Permitted Concomitant Medication and Procedures

Permitted concomitant gMG treatments include:

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

Participants receiving corticosteroids and/or NSIDs must be on a stable dose for at least 1 month before screening. Concomitant gMG treatment must be administered at a stable dose from screening through W21.

After W21, there are no restrictions on concomitant gMG therapy, and weaning off these medications is permitted. The dose of the concomitant gMG treatment should not be changed during the transition between the q2w and q3w dosing regimens.

Only vaccines that are not live- or live-attenuated vaccines are permitted. All vaccinations received during the study will be recorded as concomitant medication as described in the SoA (Section 1.3), including brand name of the vaccine and the date of vaccination, if possible. Vaccinations within 48 hours before or after IMP administration should be avoided.

6.9.3. Prohibited Medications and Procedures

The following treatments will be prohibited:

- any monoclonal antibody
- IV or SC IgG therapy, unless administered as rescue therapy (see Section 6.9.4)
- any other experimental/study IMP
- live or live-attenuated vaccines

Any change in gMG therapy during part A is also prohibited. There are no restrictions in Part B.

Participants who receive prohibited medication will be discontinued from the study after an ET visit and an SFU visit 60 ± 3 days after the participant's last dose of IMP (see Section 7.2).

Participants will not be discontinued from the study in case of a protocol deviation due to the following prohibited activities:

- increasing the dose or frequency of corticosteroids
- starting a new type of steroid
- increasing the dose or frequency of a NSID
- starting a new NSID
- increasing the dose or frequency of an AChE inhibitor
- decreasing the dose or frequency of a corticosteroid, a NSID, or an AChE inhibitor

6.9.4. Rescue Medication

Plasma exchange, IgG therapy, immunoadsorption, or a change in the dosage or type of corticosteroid are considered rescue therapy if the following conditions apply:

1. The treating physician believes that the participant's health is in jeopardy if rescue therapy is not provided.
2. The participant is deteriorating clinically as indicated by new or worsening respiratory/bulbar symptoms or a ≥ 2-point increase in any individual nonocular item on the MG-ADL scale compared with the previous visit.

The date and time of the rescue medication, the name, dosage, and frequency of the rescue medication, and the response to the rescue therapy, as measured by the MG-ADL total score, will be recorded on the eCRF. A maximum of 3 rescue therapy treatments is allowed per year. If more than 3 rescue therapy treatments are needed within 1 year, participants will be discontinued from IMP.

Participants will not be discontinued after receiving ≤ 3 rescue therapy treatments unless the investigator believes it is in the best interest of the participant.

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or the entire study are detailed in Appendix 1 (Section 10.1) .

7.1. IMP Discontinuation

7.1.1. Permanent Discontinuation

Permanent discontinuation of IMP occurs when the participant stops receiving IMP before the end of the study and does not resume receiving IMP. The participant also must not have withdrawn informed consent.

The investigator will document the primary reason for early discontinuation of IMP.

Unless consent from the study has been withdrawn, the participant will discontinue the study (refer to Section 7.2) and attend an ET visit and an SFU visit. Study sites will attempt to perform the ET visit within 7 days of the early discontinuation decision. The SFU visit will occur 60 ± 3 days after the participant's final IMP administration.

The following circumstances will result in the permanent discontinuation of IMP:

- Participant becomes pregnant or intends to become pregnant (refer to Section 8.2.7).
- Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed).
- Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of NCI-CTCAE grade 4 that is considered related to IMP by the sponsor.
- Participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship to the IMP.
- Participant receives a prohibited medication or substance (Section 6.9).
- Participant receives more than 3 rescue therapy treatments per year.

7.1.2. Temporary Discontinuation

Temporary discontinuation of IMP occurs when the participant discontinues receiving IMP before the end of the study and resumes once the cause for the discontinuation has been resolved.

Reasons for temporary discontinuation may include an AE that meets the following criteria:

- Any SAE considered related to IMP by the sponsor
- Clinically significant active infection considered related to the IMP by the sponsor

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 before its planned completion.

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. The reason for early discontinuation from the study will be clearly documented by the investigator.

Participants must discontinue the study if:

- it is in the best interest of the participant.
- the DSMB recommends discontinuation (see Section 10.1.6.1).
- the participant receives prohibited medication (see Section 6.9.3).
- a hypersensitivity reaction to the IMP occurs.
- the participant is pregnant.
- the sponsor requests discontinuation.
- IMP is permanently discontinued (refer to Section 7.1.1).

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

If a participant needs to be discontinued from the study, he or she will stop receiving efgartigimod immediately and perform an ET visit within 7 days of the early discontinuation decision. Additionally, the participant will complete a SFU visit 60 ± 3 days after his or her last dose of efgartigimod and discontinue from the study.

A SFU phone visit assessing only AEs and concomitant therapy and procedures will be performed if the participant discontinues to access IMP through an alternative source.

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, they may request destruction of any samples taken and not tested, and the investigator must document this in the study site records and inform the sponsor as soon as possible.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or 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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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 or she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

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.

Adherence to the study design requirements, including those specified in the SoA, is required for study conduct.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Operational considerations related to the COVID-19 pandemic are provided in Section 10.6.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in Section 1.3.

8.1.1. Pharmacodynamics

Total IgG levels and AChR-Abs will be measured from blood samples using validated methods. The actual date and time of the blood sample collection will be recorded and included in the central laboratory data transfer.

8.1.2. 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.

8.1.3. [redacted]

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8.1.5. [redacted]

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8.1.6. [redacted]

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8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3). Safety measures will be assessed before IMP administration unless otherwise stated.

At screening, clinically significant abnormalities in any safety assessment related to preexisting conditions will be reported as medical history. New abnormal or worsened preexisting conditions observed after screening that the investigator considers clinically significant will be reported as an AE.

8.2.1. Demographic Characteristics

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

8.2.2. Medical and Surgical History

Medical history will be recorded on the eCRF and will include:

- All relevant medical history (eg, significant findings, surgeries, and preexisting conditions present at screening), regardless of whether it is related to gMG
- Previous emergency room (ER) visits, hospitalizations, and intensive care unit (ICU) admissions from 1 year before screening, including the number of days admitted
- Abnormalities in the physical examination, vital signs, electrocardiogram (ECG), and laboratory results at screening. During the study, new or worsened abnormalities will be reported as AEs
- All available vaccine history. For vaccines where multiple doses or boosters are received, only the most recent ones must be recorded

8.2.3. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the participant's general appearance, skin, lymph nodes, musculoskeletal/extremities, cardiovascular, respiratory, gastrointestinal, and neurological systems.

- Height and weight will also be measured and recorded. Height will be measured at screening only and weight will be measured as indicated in the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- New or worsened abnormalities observed in the physical examinations during the study will be reported as AEs.

8.2.4. Vital Signs

Vital signs (to be taken before blood collection for laboratory results) will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

It is recommended that the method used to measure body temperature at screening continues to be used throughout the study.

Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will only be used 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)

8.2.5. Electrocardiograms

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

8.2.6. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing. The details of sampling, handling, storage, and transportation of samples will be described in the laboratory manual. The actual sample collection date and time must be entered in the participant's source document and on the laboratory eCRF page.

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 the investigator considers them to be more severe than expected for the participant's condition.

All laboratory tests with values considered to be clinically significantly abnormal during participation of 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 or baseline within a period of time judged to be reasonable by the investigator, the etiology should be identified and the sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, AE, SAE, or drug interruption), then the outcome of laboratory tests and the change in participant management must be recorded.

8.2.6.1. Hematology, Clinical Chemistry, and Urinalysis

The list of clinical safety laboratory parameters for hematology, clinical chemistry, and urinalysis are provided in Table 8 and Section 10.2.1.

Blood samples for the 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.

Blood samples for safety assessments will be collected according to the laboratory manual. The samples will be analyzed by the central laboratory.

Clinical laboratory tests will be reviewed for potentially significant findings at all timepoints throughout the study. Findings meeting the definition of an AE (see Section 10.3) must be recorded on the AE page of the eCRF. See Section 10.3.3 for information on following up on clinically significant abnormalities.

Laboratory tests with values considered clinically significantly abnormal during the study that meet the definition of an AE will be monitored until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

8.2.6.2. Virus Serology

For exclusion criterion 8, blood will be sampled and evaluated for virus serology as described in Section 10.2.1.

8.2.6.3. Follicle-Stimulating Hormone Levels

Female participants (except those who are surgically sterilized) must have their follicle-stimulating hormone (FSH) levels measured at screening. See Section 10.2.

8.2.6.4. SARS-CoV-2 Test

Nasal and throat mucosal cell samples will be collected according to the laboratory manual, to be tested for SARS-CoV-2. Participants can be retested as needed (Section 10.5).

8.2.7. Pregnancy Testing

Pregnancy testing at screening will be a highly sensitive serum test (see inclusion criterion b). All subsequent pregnancy testing will be done using urine tests . If local regulations require more frequent or sensitive testing, then the local regulations will be followed. Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure. See Section 1.3 and Section 8.3.4 for more details.

Additional serum or urine pregnancy tests may be performed, if determined 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

Blood samples will be collected at the time points indicated in the SoA (Section 1.3) to assess the serum levels of ADA against efgartigimod. Sampling will be done predose when performed at dosing visits.

As per regulations, all samples will be analyzed in a 3-tiered approach using validated methods:[4]

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 (tier 2). 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 (tier 3) to characterize the magnitude of the ADA response.

ADA samples will be stored for potential testing of NAbs against efgartigimod if PK/PD results are inconclusive. Any NAb testing that may occur should only be performed on ADA-positive samples confirmed in tier 2.

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

8.2.9. Suicidal Ideation and Behavior Risk Monitoring

Efgartigimod is being developed for a neurologic indication, so suicidal ideation and risk behavior (SIB) monitoring is required.

- Participants being treated with IMP will 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 IMP.
- Baseline assessment of SIB and emergent SIB will be monitored with the following question derived from the Patient Health Questionnaire (PHQ) item 9: “Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?”

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

The definitions of AEs and SAEs can be found in Section 10.3. An AESI is an AE of scientific and medical concern specific to the sponsor’s product or program and described in Section 8.3.5.

AEs (including SAEs, AESIs, and AEs of clinical interest) will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7.2).

An unexpected AE is any AE that 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. The assessment of expectedness will be the responsibility of the sponsor.

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 Appendix 3 (Section 10.3).

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 SFU as specified in the SoAs (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately as indicated in Section 10.3 and under no circumstance should this exceed 24 hours from when the site staff is aware of the SAE/AESI. The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs as defined in Section 8.3.5 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 10.3.3. 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, IRBs/IECs, and investigators.
- An investigator who receives a 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 IEC/IRB, as per applicable regulatory requirements. The sponsor (or its designee) will also be responsible to forward SUSAR reports to all investigators involved in the study, who will be required to report these SUSARs to their respective IECs/IRBs, as per their local regulatory requirements.

8.3.4. 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 IMP.
- Attempts will be made to obtain details of all pregnancies in female partners of male participants that occurred after the start of the study intervention and until 90 days after the last dose of IMP. Female partners will be asked to sign a relevant ICF.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. Contact details are provided in **Serious Adverse Event Reporting**.
- 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 (or consenting pregnant partner of a male participant, refer to Section 10.1.3) will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant or the consenting

pregnant 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, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue IMP.

8.3.5. Adverse Events of Special Interest

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program. An AESI can be serious or non-serious, related or unrelated to the IMP or study procedures. Further characterizing information will be collected on the eCRF. These events will be reported according to the same timeframe as that for SAEs specified in Section 8.3.1 and Section 10.3.4.

Efgartigimod treatment leads to reduced IgG levels. As low IgG levels can be associated with increased infection risks, events under the MedDRA SOC *Infections and infestations* are considered AESIs in this study. As such, any infections are considered AESIs in this study. These events will be reported according to the timeframe specified in Section 8.3.1 and Section 10.3.4, with the following information provided:

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

Participants for whom an AESI has been reported may be temporarily interrupted from IMP treatment, as specified in Section 7.1.2.

8.3.6. Adverse Events of Clinical Interest

8.3.6.1. Infusion/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 or IV injection, injection- or infusion-related reactions can occur during or after administration.

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

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

8.4. Pharmacokinetics

Blood samples for pharmacokinetics (PK) will be collected from each participant as specified in Section 1.3. Concentrations of efgartigimod will be determined using a validated method. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples collected for analyses of efgartigimod concentration may also be used to evaluate the safety or efficacy aspects relating to concerns arising during or after the study.
- When samples are taken on dosing days, the PK samples will be taken both predose (within 1 hour of starting the infusion) and postdose (within 1 hour after the end of the infusion). When samples are taken on nondosing days, only 1 PK sample will be taken.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers

See Section 8.1.1 for assessments of total IgG and AChR-Ab 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 on the eCRF to allow for the assessment of any changes in these parameters with IMP treatment. Historical data on these parameters from at least 12 months before starting the study will be collected at the start of the study.

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 of 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 does 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 and work instructions of the sponsor's designated CRO will be used as the default methodology if not otherwise specified.

The SAP will be finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. 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 the clinical study report(s). The following sections contain the main general features of the statistical analysis. More details will be provided in the SAP.

9.1. Statistical Hypotheses

No statistical hypotheses are being tested in this exploratory study.

9.2. Analysis Sets

The following key analysis sets are defined:

Table 6: Analysis Sets

Analysis Sets	Description
Safety analysis set	All randomized participants who are exposed to the IMP
Intention-to-treat (ITT) set	All randomized participants with an MG-ADL score at baseline and at least 1 post-baseline MG-ADL score at or before W21

Additional analysis sets, such as the per-protocol analysis set will be defined in the SAP.

9.3. Statistical Analyses

The SAP will be finalized before 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.

9.3.1. General Considerations

The baseline value will be defined as the last assessment before the first administration of IMP.

For the derivation of the primary efficacy endpoint, the actual visit date will be used.

All study visits will be recalculated based on actual dates and will be referred to as "analysis visits," which will be used in the statistical analysis except for the derivation of the primary efficacy endpoint. The rules for calculating the analysis visits will be documented in the SAP. Rules for inputting partial or missing dates will also be documented in the SAP.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Definition of the Estimand for the Primary Endpoint

- Population: ITT analysis set (see Table 6)
- Variable: mean of the average MG-ADL total score improvement during W1 through W21
- Main intercurrent events
  - Early treatment discontinuation for any reason before W21
  - Initiation of IgG therapy as rescue therapy before W21

Handling of Main Intercurrent Events

For early treatment discontinuation before W21, the mean MG-ADL total scores will be calculated for all available MG-ADL change scores between W1 and W21. If IgG therapy is administered as rescue therapy before W21, any MG-ADL total scores reported after starting rescue therapy will be excluded from the derivation of the primary efficacy endpoint.

Estimation of Treatment Effect and Statistical Inference

An analysis of covariance model (ANCOVA) will be used to estimate the mean of the average MG-ADL total score change from baseline during W1 through W21 for each treatment arm, and the 2-sided 95% confidence interval for the difference between the 2 treatment arms (mean of the average MG-ADL improvement from baseline in the cyclic regimen arm – mean of the average MG-ADL total score change from baseline in the continuous regimen arm). The model will include the treatment arm as a factor and the baseline MG-ADL total score as covariates.

9.3.3. Other Endpoint(s)/Estimand(s) Analysis

All secondary and exploratory endpoints, if applicable, will be summarized overall and by treatment arms until W21, and by dosing regimens in the extension period.

The Kaplan-Meier method will be used to analyze the time from the first q3w dose to the first q2w dose when transitioning back to the q2w regimen.

Population PK and PD analyses may be performed and will be reported separately.

9.4. Interim Analysis

An interim analysis is planned once approximately 24 participants have completed the W14 visit, and will focus on descriptive summaries of selected efficacy endpoints. No formal statistical testing will be performed for the interim analysis. There is no intention to stop the study for efficacy or to adjust the sample size based on the interim analysis data. As a result, no adjustment for multiplicity will be necessary.

A second interim analysis may be performed if there is a need for more information regarding the continuous dosing regimen before the final analysis.

The scope of each interim analysis will be specified in the SAP.

9.5. Sample Size Determination

Approximately 72 participants will be enrolled and randomized in a 3:1 ratio to either the continuous q2w treatment arm or the cyclic regimen arm. A randomization ratio of 3:1 was chosen because the cyclic regimen is well-studied in more than 150 gMG patients in the completed study ARGX-113-1704 and the ongoing extension study ARGX-113-1705.

With the given sample size of 54 participants in the continuous regimen arm and 18 participants in the cyclic regimen arm, the difference between both treatment regimens in terms of average total MG-ADL change versus baseline can be estimated with sufficient precision. Assuming a standard deviation (SD) of 2.0 in the continuous regimen arm and 2.6 in the cyclic regimen arm, then the pooled standard error (SE) is estimated to be 0.588 and the 1-sided width of the 2-sided 95% confidence interval (CI) is estimated to be 1.173.

Furthermore, 54 participants in the continuous regimen arm will allow the determination of the AE incidence rate (see Table 7 for the AE probabilities used to calculate this sample size).

Table 7: AE Probability by Incidence Rate

Incidence Rate of AE	Probability of Detecting an AE[a]
1%	42%
2%	66%
5%	94%

AE=adverse event
[a] The probability of detecting an AE is based on the incidence rate of the AE and the sample size of the study.

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 ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Independent 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 before 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 study conduct at the site and adhering to requirements of ICH guidelines, the IRB/IEC, and local laws and regulations 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 global/local insurance for the study, including the study participants, for the required duration of time.

The sponsor maintains 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 who provides informed consent will be assigned a unique participant ID via the interactive response technology system.

The investigator or their 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 their 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) (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 a participant was enrolled in the study and the date written consent was obtained. The authorized person for obtaining the informed consent must also sign the ICF.

A separate ICF will be issued in the case of pregnancy of a female partner of a male participant. If required by local regulations, a separate pregnancy ICF will be issued for female participants who become pregnant.

All participant information and ICFs must be available in the local and vernacular languages required at the site and include participant information sheets and 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 before the performance of any protocol procedures.

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

10.1.4. Recruitment Strategy

Not applicable.

10.1.5. 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 or 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 his or her data to be used as described in the informed consent.

The participant must be informed that his or 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.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

10.1.6.1. 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.

10.1.7. Dissemination of Clinical Study Data

The sponsor will register and disclose the clinical study results as required by law.

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 electronic CRF (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 investigational medicinal product (IMP) (ie, an eCRF must 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.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor (or its designee) electronically (eg, laboratory data) or via paper SAE forms. The investigator is responsible for verifying that data entries are complete, accurate, and verifiable by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF, if and where applicable. Source data verification on race and ethnicity will be performed unless local regulations do not permit it.

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.

10.1.8.1. 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 before changing the location or status of any essential clinical study documents. The investigator must contact the sponsor before 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.

10.1.8.2. 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.

10.1.8.3. 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 10.1.8.2.

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

10.1.9. 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 on 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 on the eCRF.

Study monitors will perform ongoing source data verification as described in Section 10.1.8.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

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

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

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

10.1.11. Publication Policy

All information regarding efgartigimod 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 guidelines and will be submitted in accordance with local regulations.

The results of this study can be published or presented at scientific meetings. If so, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and provide comments.

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 8 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 8: Protocol-Required Safety Laboratory Tests

Laboratory Test	**Parameter**			
Hematology	RBC	RBC indices: 1. MCV 2. MCH 3. % reticulocytes	WBC count with differential:	
	Platelet count		1. neutrophils 2. eosinophils 3. lymphocytes 4. basophils 5. monocytes	
	Hemoglobin			
	Hematocrit			
Clinical chemistry	BUN	potassium	AST	total protein
	creatinine	sodium	ALT	bilirubin (total and direct)
	glucose (fasted for 8 hours)	calcium	ALP[a]	albumin
	HbA1c	CRP	LDH	GGT
	aPTT	PTT, INR	total cholesterol	HDL
	LDL (measured)		triglycerides	
Urinalysis	1. Specific gravity 2. pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick 3. Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential, defined in Appendix 4)[b]			
Other screening tests	SARS-CoV-2 test FSH (for WOCBP, excluding surgically sterilized female participants) AChR-Ab serology Viral serology, see Section 10.2.1			

AChR-Ab=anti-acetylcholine receptor antibody; ALT=alanine aminotransferase; ALP=alkaline phosphatase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HbA1c=glycosylated hemoglobin; hCG=human chorionic gonadotropin; HDL=high-density lipoprotein; IEC=independent ethics committee; INR=international normalized ratio; IRB=institutional review board; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PTT=partial thromboplastin time; RBC=red blood cell; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WBC=white blood cell; WOCBP=women of childbearing potential

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

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

10.2.1. Other Screening Tests

10.2.1.1. Hepatitis B Virus

Patients with an active acute or chronic hepatitis B viral infection at screening cannot be enrolled in the study.

The following combinations of serologic markers will be used to identify an active hepatitis B viral infection[5]:

Table 9: Interpretation of Hepatitis B Serological Test Results

Test Result			Interpretation
HBsAg	Anti-HBc	Anti-HBs	
Positive	Positive	Negative	The patient cannot be enrolled in the study because the test results indicate an active hepatitis B viral infection.
Negative	Positive	Negative	The patient cannot be enrolled in the study because the test results indicate a low level chronic hepatitis B viral infection with impaired liver function.

anti-HBc=total hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen
Note: Interpretation is according to a medical doctor with sufficient expertise in hepatology or infectious disease. Additional tests (eg, HBV viral load) could be required to determine the participant's status.

10.2.1.2. Hepatitis C Virus

Patients with an active acute hepatitis C viral infection at screening cannot be enrolled in the study. The hepatitis C virus antibody serologic test will be used to identify an active hepatitis C viral infection as indicated in Table 10.

Table 10: Interpretation of the Hepatitis C Antibody Test

HCV Ab Test Result	Interpretation
Positive	An active acute or chronic HCV infection is exclusionary unless an RNA test indicates HCV negative.

HCV Ab=hepatitis C virus antibody

10.2.1.3. Human Immunodeficiency Virus

Patients who are HIV positive and do not have an AIDS-defining condition or a CD4 count >200 cells/mm^3 at screening can be enrolled in the study (see Table 11). Patients who are HIV positive and have an AIDS-defining condition or a CD4 count ≤ 200 cells/mm^3 at screening cannot be enrolled in the study. The following are considered AIDS-defining conditions:

- Cytomegalovirus retinitis with loss of vision
- *Pneumocystis jiroveci* pneumonia
- Chronic intestinal cryptosporidiosis

- HIV-related encephalopathy
- *Mycobacterium tuberculosis* (pulmonary or extrapulmonary)
- Invasive cervical cancer

Table 11: Interpretation of HIV Test Results in Combination With the Patient's Clinical Condition and CD4 Count

HIV Test Result	Clinical Condition or CD4 Count	Interpretation
Positive	AIDS-defining condition is present or CD4 count $\leq$ 200 cells/mm^3	The patient cannot be enrolled in the study because test results and clinical condition or CD4 count confirm the diagnosis of AIDS.

AIDS=acquired immune deficiency syndrome; HIV=human immunodeficiency virus

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An adverse event (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, electrocardiogram [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 preexisting condition including either an increase in frequency and/or intensity of the condition
- New condition 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/serious adverse event (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 that 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted 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 serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline will not be collected as an AE.

d. 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 one 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.
- Suspected transmission of any infectious agent via the IMP will also be treated as an SAE.

10.3.3. 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 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 or 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 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 one 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 IMP and each occurrence of each AE/SAE as **related** or **not related**. The investigator will use clinical judgment to determine whether there is reasonable possibility that the IMP caused the AE.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP administration is compelling and/or follows a known or suspected response pattern concerning that IMP.
- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP and the AE.

The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his or her assessment.

For each AE/SAE, the investigator **must** document in the medical notes that he or 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 or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 by 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 postmortem findings including histopathology.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper Data Collection Tool

- All SAEs and AESIs will be recorded on the AE form in the electronic case report form (eCRF). SAEs will also be recorded on the paper SAE report form. The investigator or designated study staff should check that all data entered are consistent.
- An alert email for the SAE and AESI reports on the eCRF will automatically be sent by email to the sponsor's or designee's safety mailbox via the electronic data capture system.
- The paper SAE report form should be faxed or emailed to the sponsor's designee (refer to the **Serious Adverse Event Reporting** details on page 2 of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Woman of Childbearing Potential

A female is considered a WOCBP unless she is either:

a. Postmenopausal: Continuous amenorrhea for at least 1 year without an alternative medical cause with a follicle-stimulating hormone (FSH) measurement of >40 IU/L. If a postmenopausal woman is using hormonal therapy, such as hormone replacement therapy or hormonal contraceptives, FSH levels might be suppressed and therefore an FSH test to confirm a postmenopausal state is not considered valid. In this case, the postmenopausal state will need to be assessed by the investigator.
b. Surgically sterilized: Documented permanent sterilization procedure (eg, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for Women of Childbearing Potential

WOCBP must use 1 of the following contraception methods from the signing of the ICF until the last IMP dose, which should be maintained at minimum until 90 days after the last dose of IMP.

The following Clinical Trials Facilitation and Coordination Group[6] methods are permitted for efgartigimod studies (see Section 10.7 for country-specific requirements): are:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

10.4.2.2. Male Contraception

No male contraception is required.

10.5. Appendix 5: Administrative Information

A list of vendors being used for the study can be found in the investigator site file.

10.6. Appendix 6: Possible Adaptations to Protocol Due to the 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 efficacy of different dosing regimens of IMP. 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 γ (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 intravenous (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. 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, as are individuals testing positive for SARS-CoV-2 (see Section 5.2). If at any point a participant tests positive for SARS-CoV-2, the administration of IMP may be temporarily discontinued until the participant's symptoms have resolved and they no longer test positive for SARS-CoV-2. Furthermore, administration of IMP to a participant will be interrupted if a clinically significant infection occurs. Infections are also considered an adverse event of special interest (AESI) subject to structured safety reporting and a detailed questionnaire, so a participant contracting COVID-19 would be recorded as an AESI.

Off-site administration by a home nurse is permitted for many of the dosing visits, depending on local regulations (see Section 10.7 for country-specific requirements). The home nurse, who will go to the participant for off-site visits, can be another person qualified to perform all tasks (eg, a

trained qualified physician), if applicable per local regulations. Thus, the number of necessary on-site visits is minimal, reducing the risk of contracting COVID-19 to participants and site staff.

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 contract research organization (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 indicated in the schedule of activities (SoA; Section 1.3) 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 before 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 an individual tests positive for COVID-19 at the start of the study, they cannot participate in the study. If a participant is infected with SARS-CoV-2 during the study, they cannot be (re)treated until they no longer test positive for SARS-CoV-2.

10.6.3.3. Study Protocol Changes

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.

10.7. Appendix 8: Country-Specific Requirements

10.7.1. France-specific Requirements

Participants will be monitored for at least 1 hour after the end of the infusion (refer to Section 1.3 Table 1, Table 2, and Section 2.3.1).

All infusion visits must occur at the study site (refer to Section 1.3 Table 1, Table 2, and Section 10.6.2).

10.7.2. Germany-specific Requirements

Sexually active male participants and their female partner of childbearing potential must use highly effective double contraception methods, which are a condom for the male participant and a highly effective form of contraception for the female partner of childbearing potential (same as for WOCBP described in Section 10.4.2.1)

Sexually active female participants of childbearing potential must use highly effective contraception methods.

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 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
    a. 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.
    b.
    c. 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

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