TITLE PAGE

Protocol Title:	A Randomized, Double-Blinded, Placebo-Controlled, Phase 3, Parallel-Group Design Study Evaluating the Efficacy and Safety of Efgartigimod IV in Adult Participants With Acetylcholine Receptor Binding Antibody Seronegative Generalized Myasthenia Gravis
Protocol Number:	ARGX-113-2308
Version Number:	3.0 (Amendment 2)
Compound:	Efgartigimod
Study Phase:	3
Sponsor Name:	argenx BV
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Regulatory Agency Identifier Number(s):	IND number [redacted] EU-CT number 2024-511796-15-00
Approval Date:	23 Sep 2024
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SIGNATURE OF THE SPONSOR

Protocol Title:	A Randomized, Double-Blinded, Placebo-Controlled, Phase 3, Parallel-Group Design Study Evaluating the Efficacy and Safety of Efgartigimod IV in Adult Participants With Acetylcholine Receptor Binding Antibody Seronegative Generalized Myasthenia Gravis
Protocol Number:	ARGX-113-2308

Sponsor Signatory:

Refer to the appended signature page

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

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read the protocol for study ARGX-113-2308.

Title: A Randomized, Double-Blinded, Placebo-Controlled, Phase 3, Parallel-Group Design Study Evaluating the Efficacy and Safety of Efgartigimod IV in Adult Participants With Acetylcholine Receptor Binding Antibody Seronegative 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 the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for 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 _____
Institution _____
Address _____
(please handprint or type) _____

Signature _____

Date _____

Protocol Amendment Summary of Changes

Global protocol document history	Date
Amendment 2 v3.0	23 Sep 2024
Amendment 1 v2.0	03 Sep 2024
Original v1.0	14 Feb 2024

Amendment 2 (23 Sep 2024)

This amendment is considered substantial based on the definition in article 2 §2 (13) of the Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary reason for this amendment is to comply with the EU-CTR assessment.

Bold font indicates new text, and ~~strikethrough~~ font indicates deleted text.

Section	Change in study conduct or planned analysis	Brief rationale
4.1. Overall Design	All participants in part B will receive open-label efgartigimod IV. During part B from C3 onward, TPs can be initiated earlier at the discretion of the investigator ~~with a minimum of 7 days between the last efgartigimod infusion in a cycle, Cn, and the first efgartigimod infusion in the next cycle, Cn+1. The participant must have enough time remaining in the study to complete the TP and the EoS~~. **The participant must meet all of the following criteria to be eligible for retreatment:** • **The participant completed the previous TP** **[…]** • **There must be at least 4 weeks left in the study for the participant, so that a full TP and the EoS visit can be performed.**	Criteria for retreatment was included

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Expansion
AChE	acetylcholinesterase
AChR	acetylcholine receptor
AChR-Ab	anti-acetylcholine receptor antibody
ADA	antidrug antibody(ies)
ADL	activities of daily living
AE	adverse event
AESI(s)	adverse event(s) of special interest
AUEC	area under the efficacy curve
Cn	cycle number
CMI	clinically meaningful improvement
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DEICT	diversity, equity, and inclusion in clinical trials
ECn	exclusion criterion (number)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDV	early discontinuation visit
EEA	European Economic Area
EFG	efgartigimod
efgartigimod IV	efgartigimod formulation for IV administration
eGFR	estimated glomerular filtration rate
EoS	end of study visit
ER	emergency room
FcRn	neonatal crystallizable fragment receptor
FSH	follicle-stimulating hormone
GCP	good clinical practice
gMG	generalized myasthenia gravis
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Expansion
IB	investigator's brochure
ICn	inclusion criterion (number)
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgG	immunoglobulin γ
IMP	investigational medicinal product
IP	intertreatment period
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
LRP4	low-density lipoprotein receptor-related protein 4
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	myasthenia gravis composite
MGFA	Myasthenia Gravis Foundation of America
[redacted]	[redacted]
MG-QoL15r	Myasthenia Gravis Quality of Life–15 revised
MMRM	mixed model repeated measures
MSE	minimal symptom expression
MuSK	muscle-specific kinase
MuSK-Ab	anti-MuSK antibody(ies)
NAb	neutralizing antibody(ies)
NCI	National Cancer Institute
NMJ	neuromuscular junction
NSIST	nonsteroidal immunosuppressive therapy
PBMC	peripheral blood mononuclear cells

Abbreviation	Expansion
PBO	placebo
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire item 9
PK	pharmacokinetic(s)
PLEX	plasma exchange
QMG	quantitative myasthenia gravis
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RNS	repetitive nerve stimulation
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCIg	subcutaneous immunoglobulin
SFEMG	single fiber electromyography
SFV	safety follow-up visit
SIB	suicidal ideation or behavior
SoA	schedule of activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TP	treatment period
TSQM-9	Treatment Satisfaction Questionnaire for Medication–9 items
UNS	unscheduled visit
VAS	visual analog scale
WOCBP	women of childbearing potential

Definitions of Terms

Cycle, Treatment Period, and Intertreatment Period

A cycle (C) is composed of a treatment period (TP) and an intertreatment period (IP).

- TP is defined as the 3-week period when participants receive IMP once weekly for 4 infusions.
- The IP is defined as the period between TPs. It is fixed in the double-blinded, placebo-controlled part A and for the first 2 cycles in the open-label part B:
  - IP is 5 weeks in part A and denoted as follow-up.
  - IP is 4 weeks in part B for the first 2 cycles (ie, C1 and C2).
  - IP is of variable duration from C3 (part B) onward, although no shorter than 7 days after the previous cycle's last efgartigimod IV infusion, depending on the participant's clinical status.

Cohorts

In the context of analysis by cohorts, cohort n is defined as all participants in at least n efgartigimod IV cycles.

MG-ADL Responder

A participant will be considered an MG-ADL responder if there is a ≥2-point reduction in the MG-ADL total score compared to baseline that is maintained for the next 4 consecutive weeks (ie, 5 consecutive visits total), with the first reduction occurring no later than 1 week after the last administration of IMP in part A.

Early MG-ADL Responder

An early MG-ADL responder has onset of MG-ADL response no later than 2 weeks after the first administration of IMP in part A.

QMG Responder

A participant will be considered a QMG responder if there is a ≥3-point reduction in the QMG score compared to baseline and maintained for the next 4 consecutive weeks (ie, 5 consecutive visits total), with the first reduction occurring no later than 1 week after the last administration of IMP in part A.

Part A+B

Part A+B refers to efgartigimod IV data from participants receiving efgartigimod IV in part A combined with data from all participants in part B regardless of treatment assignment in part A.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-Blinded, Placebo-Controlled, Phase 3, Parallel-Group Design Study Evaluating the Efficacy and Safety of Efgartigimod IV in Adult Participants With AChR-Ab Seronegative gMG

EU CT: 2024-511796-15-00

Rationale: Increasing evidence suggests that in all subtypes of acquired acetylcholine receptor binding antibody (AChR-Ab) seronegative generalized myasthenia gravis (gMG), the disease is immunoglobulin γ (IgG)-mediated. Also, there are few evidence-based treatment options as this patient population has been traditionally excluded from clinical studies. The high unmet medical need and growing evidence of the pathogenic role of IgG autoantibodies in this gMG population have prompted the evaluation of efgartigimod in AChR-Ab seronegative patients with gMG.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To determine the efficacy of efgartigimod IV compared to placebo in participants with AChR-Ab seronegative gMG in part A	• Myasthenia Gravis Activities of Daily Living (MG-ADL) total score change from baseline to day 29 (ie, 7 days after the fourth administration; week 4) in part A
Secondary	**Key secondary (hierarchical testing)**
To determine the efficacy of efgartigimod IV compared to placebo, and the long-term efficacy of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Quantitative myasthenia gravis (QMG) total score change from baseline to day 29 in part A • Proportion of participants who are both MG-ADL and QMG responders in part A
	Other Secondary (nonhierarchical testing)
	• Proportion of participants with MSE (defined as an MG-ADL total score of 0 or 1) • Proportion of participants who are MG-ADL responders in part A • Proportion of participants who are QMG responders in part A • Proportion of participants who are early MG-ADL responders in part A • MG-ADL total score actual value and change from baseline over time in part A and part A+B • QMG total score actual value and change from baseline over time in part A and part A+B • MG-QoL15r score change from baseline to day 29 in part A • MG-QoL15r actual values and change from baseline over time in part A and part A+B • EQ-5D-5L VAS actual value and change from baseline over time in part A and part A+B

Objectives	Endpoints
To assess the safety and tolerability of efgartigimod IV compared to placebo and the long-term safety and tolerability of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Incidence and severity of AEs and SAEs in part A and part A+B • Clinically relevant changes in laboratory parameters, ECGs, and vital signs in part A and part A+B
To assess the PD effect of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Total IgG concentrations actual values and percent changes from baseline over time in part A and part A+B

Primary Estimand:

Population:	Adult patients with AChR-Ab seronegative gMG
Endpoint:	Change from baseline at day 29 in the MG-ADL total score
Treatment condition	IMP (efgartigimod IV vs placebo)
Intercurrent events:	Initiating rescue therapy before day 29 Discontinuing IMP for any reason
Population-level summary:	Difference in mean change between treatment conditions

Overall Design: Adult participants (at least 18 years of age) with AChR-Ab seronegative gMG whose MG diagnosis has been confirmed by an MG diagnostic adjudication committee will be stratified by MuSK-Ab status and randomized within each stratum in a 1:1 ratio to receive double-blinded IMP, either efgartigimod IV 10 mg/kg or placebo in part A. Participants completing part A will enter part B and receive open-label efgartigimod IV.

Brief Summary: The primary purpose of this study is to measure the efficacy and safety of efgartigimod IV compared to placebo in participants with AChR-Ab seronegative gMG. Other objectives are to assess long-term efficacy, safety, and tolerability of efgartigimod.

Number of Participants: Approximately 110 participants are randomized in a 1:1 ratio to either the efgartigimod IV (10 mg/kg, 1-hour infusion) or placebo (placebo solution, 1-hour infusion). Note: Enrolled means the participant agrees to participate in the clinical study by completing the informed consent process.

Study Arms and Duration: The study will comprise of a screening period of up to 5 weeks, Part A and Part B as described below:

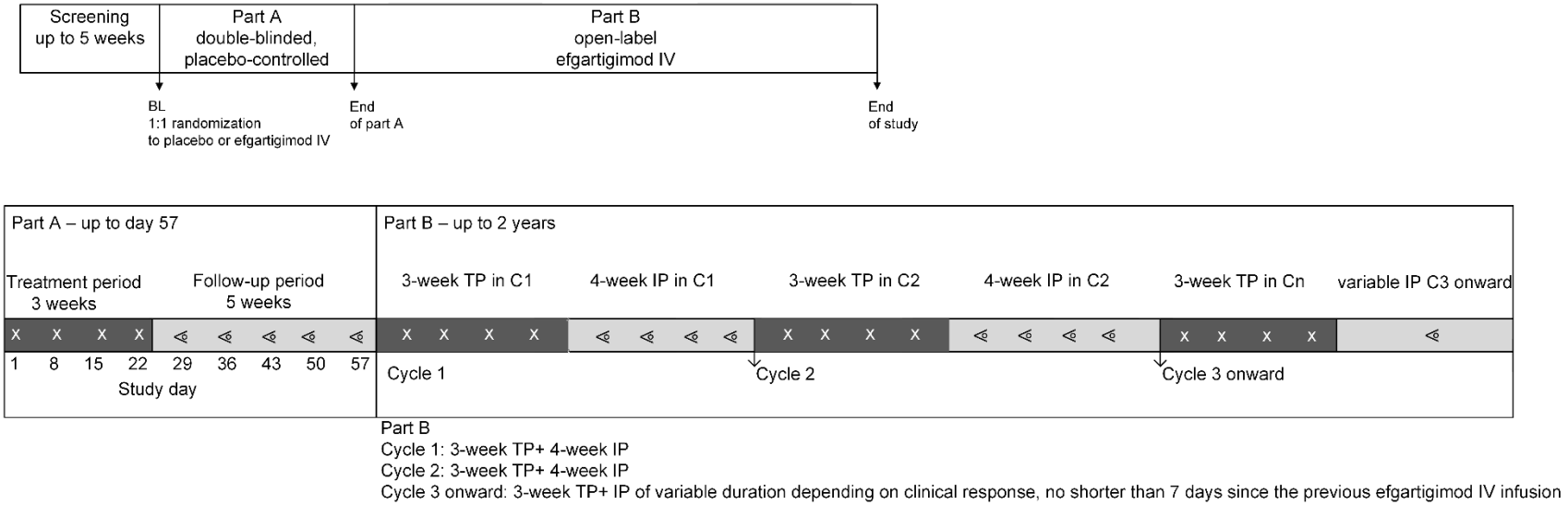
Part A (8 weeks)	Composed of a single treatment period (TP) (3-week TP of once weekly IMP infusions [4 total]) and intertreatment period (IP) (5-week follow-up period) grouped as a single cycle
Part B (up to 2 years)	Composed of TPs and IPs grouped in cycles (Cn=TPn+IPn): 3-week TP and 4-week IP for C1 and C2; 3-week TP and IP of indeterminant length based on participant clinical status, no shorter than 7 days after the cycle's last efgartigimod IV infusion from C3 onwards

Data Monitoring/Other Committee: Yes

Ethical Considerations: The favorable benefit-risk profile of efgartigimod IV 10 mg/kg IV has been well-established in the postmarketing setting and clinical studies conducted to date. There are potential risks and discomforts associated with being in the study. The anticipated benefits justify these risks. The informed consent form will advise participants of the risks.

1.2. Schema

Figure 1: ARGX-113-2308 Study Design



≪=monitoring; BL=baseline; C=cycle; Cn=Cycle n; efgartigimod IV=efgartigimod for IV administration; IP=intertreatment period; IV=intravenous; TP=treatment period; X=infusion

1.3. Schedule of Activities

Table 1: Part A – Double-Blinded, Placebo-Controlled Period

	SCN[a]	Treatment period				Follow-up period				End of part A[b]	UNS[c]	
Study visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**			
Study week		**BL**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**		
Study day (window)	**-35 to -1**	**D1**	**D8 (+1)**	**D15 (+1)**	**D22 (+1)**	**D29 (±2)**	**D36 (±2)**	**D43 (±2)**	**D50 (±2)**	**D57 (±2)**	**NA**	**Protocol section**
Eligibility/BL only												
Informed consent[d]	X											10.1.3
Medical history[e]	X											8.1, 8.3
Demography	X											
Weight/height[f]	X	X								X	(X)	6.6, 8.3.1
Viral screening[g]	X											5.2, 10.2.1
Serology[h]	X											10.2
Eligibility check	X	X										5.1, 5.2, 5.4, 8.1.1
Randomization		X										6.3
Efficacy												
MG-ADL[i]	X	X	X	X	X	X	X	X	X	X	X	8.2.1
QMG[j]		X	X	X	X	X	X	X	X	X		8.2.2
MGC		X	X	X	X	X				X		8.2.3
[redacted]	[redacted]											
MG-QoL15r		X				X				X		8.2.5

	SCN[a]	Treatment period				Follow-up period				End of part A[b]	UNS[c]	
Study visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**			
Study week		**BL**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**		
Study day (window)	**-35 to -1**	**D1**	**D8 (+1)**	**D15 (+1)**	**D22 (+1)**	**D29 (±2)**	**D36 (±2)**	**D43 (±2)**	**D50 (±2)**	**D57 (±2)**	**NA**	**Protocol section**
Neuro-QoL Short Form – Fatigue		X	X	X	X	X				X		8.2.6
PGI-S		X		X		X				X		8.2.7
PGI-C				X		X				X		
EQ-5D-5L		X				X				X		8.2.8
TSQM-9		X				X						8.2.9
Safety												
Physical examinations[k]	X	X								X	X	8.3.1
Vital sign measurements[l]	X	X	X	X	X	X		X		X	X	8.3.2
ECG	X									X		8.3.3
Pregnancy testing [m]	X	X	X	X	X					X	X	8.3.5
PHQ-9 for SIB	X	X				X				X		8.3.6
Blood sampling												8.1.2 8.3.4 10.2
Clinical laboratory testing, including urinalysis	X	X		X		X		X		X	X	
PK[n]		X	X	X	X	X						8.5
PD[o]	X	X	X	X	X	X		X		X		8.6
Biomarkers[p]		X				X		X		X		8.8
Immunogenicity		X		X		X				X		8.9

	SCN[a]	Treatment period				Follow-up period				End of part A[b]	UNS[c]	
Study visit		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**			
Study week		**BL**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**		
Study day (window)	**-35 to -1**	**D1**	**D8 (+1)**	**D15 (+1)**	**D22 (+1)**	**D29 (±2)**	**D36 (±2)**	**D43 (±2)**	**D50 (±2)**	**D57 (±2)**	**NA**	**Protocol section**
IMP infusion[q]		X	X	X	X							6
AE[r]	Continuous monitoring											8.4, 10.3
Concomitant therapy[r]	Continuous monitoring											6.9
Health economics[r]	Continuous monitoring											8.10

(X)=flexible activity, performed as needed; AChE=acetylcholinesterase; AChR-Ab=anti-acetylcholine receptor antibody; AE=adverse event; BL=baseline; D=day; ECG=electrocardiogram; ICF=informed consent form; IgG=immunoglobulin gamma; IMP=investigational medicinal product; IV=intravenous(ly); LRP4=low-density lipoprotein receptor-related protein 4; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; [redacted] MG-QoL15r=Myasthenia Gravis Quality of Life–15 revised; MuSK=muscle-specific kinase; MuSK-Ab=anti-MuSK antibody(ies); NA=not applicable; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic(s); PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire item 9; PK=pharmacokinetic(s); QMG=Quantitative Myasthenia Gravis; QoL=quality of life; SCN=screening; SIB=suicidal ideation or behavior; TP=treatment period; TSQM-9=Treatment Satisfaction Questionnaire for Medication–9 items; UNS=unscheduled visit; V=visit; W=week; WOCBP=women of childbearing potential

Note**: All activities will be performed predose on dosing days**, unless otherwise indicated. Country-specific differences relevant to any parameter in the schedule of activities are described in Section 10.8.

[a] Scenarios that could result in a prolongation of the up to 5-week screening period are described in Section 5.4 and Section 8.1.1.

[b] Participants will start part B upon completion of part A. The end of part A visit and part B TP_1V1 will occur on the same day.

[c] A UNS visit may occur at the investigator or participant's request. Depending on the reason for the UNS visit, the activities indicated will be performed at the investigator's discretion. Required activities include vital sign measurements, brief physical examination, pregnancy test for WOCBP, and MG-ADL.

[d] Only after the participant provides informed consent can any other study-related activity occur.

[e] Medical history is the participant's family history and health history, including relevant prior therapies and surgeries, all emergency room visits, hospitalizations, and admissions to intensive care units during the prior 12 months. All available vaccination history will be recorded, with the most recent vaccination for those with multiple doses or boosters.

[f] Height will be measured only at screening. Participants may be reweighed any time a change in weight is detected per Section 6.6.

[g] Retesting for virology may occur as needed.

[h] Serology for eligibility includes total IgG and AChR-Ab, and anti-MuSK antibodies for stratification. A sample to evaluate anti-LRP4 antibodies will also be collected, but the results are unnecessary for inclusion.

[i] Once enrolled, the participant must complete the MG-ADL before any other activity.

[j] AChE inhibitors must be withheld for at least 12 hours before the QMG assessment.
[k] A complete physical examination will be conducted at screening and at the end of part A visit (D57); a brief physical examination will be conducted at baseline. A symptom-directed physical examination is allowed at visits when no physical examination is required.
[l] Maintaining the same method used to measure a participant's body temperature at baseline is recommended throughout the study.
[m] WOCBP will be evaluated for pregnancy using a serum pregnancy test at screening and a urine pregnancy test at all other time points. A negative pregnancy test result must be confirmed before the IMP infusion. Pregnancy testing may be repeated as necessary.
[n] Blood samples for PK analysis will be collected before the infusion and within 1-hour postinfusion on IMP administration days.
[o] The PD analysis comprises total IgG concentration [redacted]
[p] Serum and plasma will be collected for biomarker analysis. A whole blood sample to isolate PBMCs will only be collected at V1 (BL), V5 (D29), and D57 (end of part A visit).
[q] IMP will be administered as an IV infusion over 1 hour. Participants will remain at the site for at least 30 minutes after the infusion for safety monitoring.
[r] AEs, concomitant and rescue therapies, medical procedures, vaccines, emergency room visits, hospitalizations, and admissions to intensive care units will be recorded from the time the ICF is signed until the last study-related activity.

Table 2: Part B - Open-Label Period

	Cycles 1 and 2			Cycle 3 onward[a]				EDV[b] EoS SFV	UNS[c]	
Study period	TP 1 and 2		IP 1 and 2	TPn (n=3 onward)		IPn (n=3 onward)				
Study visit[d]	V1[e]	V2/V3/V4	V1	V1	V2/V3/V4	V1	Vm			
Study day (window)	A	A+7/14/21 (±2)	A+28 (±2)	A	A+7/14/21 (±2)	A+28 (±2)	Y+21[f] (±7)	NA	NA	Protocol section
Efficacy										
MG-ADL[g]	X	X	X	X		X	X	X	X	8.2.1
QMG[h]	X	X	X							8.2.2
MGC	X	X	X	X	X (only V4)		X[i]	X		8.2.3
[redacted]										
MG-QoL15r	X		X	X		X	X	X		8.2.5
Neuro-QoL short form Fatigue	X		X	X		X	X	X		8.2.6
PGI-S	X	X (only V3)	X							8.2.7
PGI-C	X	X (only V3)	X							
EQ-5D-5L	X		X	X			X[i]	X		8.2.8
TSQM-9[j]			X (only IP2)	(X)	(X)	(X)	(X)	X		8.2.9
Safety										
Physical examination[k]	X		X	X			X[i]	X	X	8.3.1
Weight	(X)			(X)					(X)	6.6, 8.3.1
Vital sign measurements[l]	X		X	X			X[i]	X	X	8.3.2
ECG	X			X			X[i]	X		8.3.3
Pregnancy testing[m]	X			X			X[i]	X	X	8.3.5
PHQ-9 for SIB	X			X				X		8.3.6

	Cycles 1 and 2			Cycle 3 onward[a]				EDV[b] EoS SFV	UNS[c]	
Study period	**TP 1 and 2**		**IP 1 and 2**	**TPn (n=3 onward)**		**IPn (n=3 onward)**				
Study visit[d]	**V1[e]**	**V2/V3/V4**	**V1**	**V1**	**V2/V3/V4**	**V1**	**Vm**			
Study day (window)	**A**	**A+7/14/21 (±2)**	**A+28 (±2)**	**A**	**A+7/14/21 (±2)**	**A+28 (±2)**	**Y+21[f] (±7)**	**NA**	**NA**	**Protocol section**
Blood sampling										8.1.2 8.3.4 10.2
Clinical laboratory testing, including urinalysis	X		X	X			X[i]	X	X	
PD[n]	X		X							8.6
Biomarkers[o]	X		X			X[o]		X		8.8
Immunogenicity	X			X			X[i]	X		8.9
Efgartigimod IV infusion[p]	X	X		X	X					6
AE[q]	Continuous monitoring									8.4, 10.3
Concomitant therapy[q]	Continuous monitoring									6.9
Health economics[q]	Continuous monitoring									8.10

(X)=flexible activity, performed as needed; A=visit day; AE=adverse event; ECG=electrocardiogram; EDV=early discontinuation visit; EoS=end of study visit; IgG=immunoglobulin gamma; IP=intertreatment period; IPnVm=Vm in IPn (intertreatment period number) visit (visit number); IV=intravenous(ly); MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; [redacted] MG-QoL15r=Myasthenia Gravis Quality of Life–15 revised; MuSK-Ab=anti-MuSK antibody(ies); PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic(s); PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire item 9; QMG=Quantitative Myasthenia Gravis; QoL=quality of life; SIB=suicidal ideation or behavior; SFV=safety follow-up visit; TP=treatment period; TPnVm=TP (treatment period number) visit (visit number); TSQM-9=Treatment Satisfaction Questionnaire for Medication–9 items; UNS=unscheduled visit; Vn=visit number; W=week; WOCBP=women of childbearing potential; x=can be 0 or higher; Y=prior IP visit

Note: **All activities will be performed predose on dosing days**. Country-specific differences relevant to any parameter in the schedule of activities are described in Section 10.8.

[a] Participants requiring retreatment from C3 onwards may begin another treatment period (ie, from TP4+xV1) at any IP visit if ≥7 days have elapsed since their last efgartigimod infusion in the prior cycle and enough time remains in the study to complete the TP and EoS. The evaluation for retreatment will occur before any scheduled activities for IPnV1/m to ensure the proper activities are performed based on the participant's clinical status (ie, those listed for IPnV1/m or TPn+1V1).

[b] The activities for participants discontinuing efgartigimod early will depend on the visit when discontinuation occurred. Participants who withdraw from the study should perform planned activities for the EDV if 56 (±3) days have not elapsed since the last dose. These participants will no longer receive efgartigimod infusions and will return for the SFV 56 ±3 days after their final infusion. If 56 ±3 days have already elapsed since the last infusion, the EDV becomes the SFV and the SFV activities must be performed. Participants who withdraw from the study between visits should attend the SFV at least 56±3 days after their final infusion. If 56 ±3 days have already elapsed since that infusion, the SFV will be planned as soon as possible.

[c] A UNS may occur at the investigator or participant's request. The activities indicated for this visit will depend on the reason for the UNS at the investigator's discretion. Required activities are vital signs, brief physical examination, pregnancy test for WOCBP, and MG-ADL.

[d] Mandatory on-site visits are all TP visits, IP1V1, IP2V1, IP3V1, EDV, EoS, SFV, and every fifth visit in the IP (eg, IPnV5, IPnV10, etc). All other visits may occur by phone.

[e] Except for the efgartigimod infusion that occurs at part B TP1V1, the end of part A visit and the part B TP1V1 assessments are identical and completed once.

[f] The timing of IPnVm is relative to the previous visit (eg, IPnV2 is 21 days after IPnV1 [Y]).

[g] The MG-ADL is recommended to be completed before any other study activity on days when it is assessed.

[h] AChE inhibitors must be withheld for at least 12 hours before the QMG assessment.

[i] Activities are to be performed only at on-site visits (every 5 visits [eg, IPnV5, IPnV10, etc...]).

[j] The TSQM-9 will be completed at IP2V1 and at the study visit closest to 1 year after BL. Site visits should not be scheduled solely to complete this questionnaire.

[k] A brief physical examination will be conducted. A symptom-directed physical examination is allowed at visits when no physical examination is required.

[l] Maintaining the same method used to measure a participant's body temperature at baseline is recommended throughout the study.

[m] WOCBP will be tested for pregnancy using urine collected for the urinalysis. A negative pregnancy test result must be confirmed before IMP administration infusion. Pregnancy testing may be repeated as necessary.

[n] The PD analysis comprises levels of total IgG [redacted]

[o] Serum and plasma will be collected for biomarker analysis. A whole blood sample will be collected to isolate PBMCs only at the IP3V1 on-site visit and the EoS, per local regulations (refer to Section 10.8).

[p] Efgartigimod IV will be administered as an IV infusion over 1 hour at V1, V2, V3, and V4 in a TP. Participants will remain on-site for at least 30 minutes after the end of the infusion for safety monitoring.

[q] AEs, concomitant and rescue therapies, medical procedures, vaccines, emergency room visits, hospitalizations, and admission to intensive care units will be recorded from the time the ICF is signed until the last study-related activity.

2. INTRODUCTION

Efgartigimod is a human IgG1-derived Fc fragment, which is a natural FcRn ligand. Engineered for increased FcRn affinity at both physiological and acidic pH, efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated recycling of IgGs and resulting in increased IgG degradation.

Efgartigimod is being evaluated for severe autoimmune diseases mediated by pathogenic IgG autoantibodies, including gMG.

2.1. Study Rationale

The AChR-Ab seronegative gMG population is heterogeneous and includes patients with autoantibodies targeting MuSK and antigens other than AChR at the neuromuscular junction.

Increasing evidence suggests that in all subtypes of acquired AChR-Ab seronegative gMG, the disease is IgG-mediated.[1,2,3,4] Treatment for these patients is predominantly used off-label and efficacy has not been proven for immunosuppressive treatments such as corticosteroids and nonsteroidal immunosuppressives.[5,6] Currently, efgartigimod is not approved for AChR-Ab seronegative patients with gMG in the US and Europe, and an approved specific immunomodulatory therapy is an identified unmet medical need for patients afflicted with this disease.

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.[7] Generalized muscle weakness results in mobility, speech, swallowing, vision, and respiration difficulties. Up to 20% of patients develop potentially life-threatening myasthenic crises involving respiratory failure requiring mechanical ventilation.[8,9]

Approximately 80% of patients with MG have detectable antibodies against the AChR in sera, and these patients are diagnosed with AChR-Ab seropositive gMG. The remaining approximately 20% of patients with gMG do not have antibodies directed against AChR and are referred to as AChR-Ab seronegative MG.[10] These patients may have detectable autoantibodies targeting other NMJ proteins, such as MuSK and LRP4, and other epitopes. Anti-MuSK antibodies are detected in 1% to 10% of patients with MG.[11] Anti-LRP4 antibodies are not as commonly identified, although they have been detected in approximately 19% of patients with gMG who are AChR-Ab seronegative and MuSK-Ab seronegative.[12] Some patients with gMG do not have autoantibodies detectable on commercially available assays; however, approximately 4% to 66% of patients for whom AChR-Ab was not detected in commercially available assays have detectable autoantibodies on more sensitive cell-based assays that are not widely available for routine clinical testing.[13,14,10,15,16,17] Other patients are thought to have autoantibodies that are either undetectable on available assays, at a lower concentration than the assay's lower limit of detection, or against epitopes that bind an unknown target. In all known subgroups of acquired AChR-Ab seronegative MG, the disease is considered IgG mediated.[1,18,2,3]

Evidence supports that AChR-Ab seronegative gMG shares similar clinical features with AChR-Ab seropositive gMG, although patients with MuSK-MG might have more severe disease with more prominent bulbar symptoms.[19,20] Furthermore, the natural history of the disease is generally similar between AChR-Ab seropositive and seronegative patients.[8,19,20,21] Muscle biopsies have shown loss of AChR in AChR-Ab seronegative patients with gMG, as seen in AChR-Ab seropositive patients.[10,22] More recent evidence in skeletal muscle from AChR-Ab seronegative patients with MG showed consistent evidence of complement deposits and IgG1 colocalized at motor-endplates, similar to that in patients with AChR-Ab seropositive MG.[23] These findings support the hypothesis that AChR-Ab seronegative patients with gMG also have IgG-mediated disease, consistent with the clinical benefit observed in efgartigimod studies.[24] Additionally, AChR-Ab seronegative patients with gMG who do not have known autoantibodies have been treated successfully with PLEX,[4] further strengthening the IgG-mediated disease etiology.

AChR-Ab seronegative gMG represents a heterogeneous patient population.[25] While treatment approaches for AChR-Ab seronegative patients are similar to those for AChR-Ab seropositive patients, evidence-based treatment options for AChR-Ab seronegative patients are limited because this patient population has been traditionally excluded from clinical studies. Recent evidence suggests clinical outcomes for AChR-Ab seronegative patients are worse than for AChR-Ab seropositive patients.[26,27] Additionally, compared to AChR-Ab seropositive patients with gMG, a longer time to diagnosis and poorer QoL were reported for AChR-Ab seronegative patients.[28] Furthermore, patients with MuSK-MG may respond differently to standard MG therapy, such as IVIg and pyridostigmine, compared to AChR-Ab seropositive patients.[19,29] These findings support the existing disease burden and substantial unmet need for AChR-Ab seronegative patients with gMG.

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 IV has been well tolerated across studies in different indications and has an acceptable safety profile.

Table 3: Potential Risks and Mitigation Strategies

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk for infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.4.6). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
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.	Monitor participants for clinical signs and symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7). If a reaction occurs, administration should be interrupted, and appropriate supportive measures instituted based on the severity of the reaction. Once resolved, administration may be cautiously resumed based on clinical evaluation.

AE=adverse event; AESI=adverse event of special interest; IgG=immunoglobulin G; IMP=investigational medicinal product

2.3.2. Benefit Assessment

Efgartigimod has shown clinical benefit in completed studies in participants with AChR-Ab seropositive gMG, which supports continued clinical investigations in other IgG-mediated conditions. In clinical studies ARGX-113-1704, ARGX-113-1705, ARGX-113-2001, and ARGX-113-2002, AChR-Ab seronegative participants with gMG treated with efgartigimod showed similar clinical efficacy and safety compared to those with AChR-Ab seropositive gMG.[30] However, the percentage of MG-ADL responders in the placebo group was unexpectedly higher in AChR-Ab seronegative participants than in AChR-Ab seropositive participants. The available clinical data support the clinical benefit of efgartigimod for reducing pathogenic IgG autoantibodies, which may improve symptoms in patients with AChR-Ab seronegative gMG.

2.3.3. Overall Benefit-Risk Conclusion

The potential risks associated with efgartigimod are justified by the anticipated benefits that may be afforded to participants with AChR-Ab seronegative gMG in this study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Primary and Key Secondary Objective

- To determine the efficacy of efgartigimod IV compared to placebo in participants with AChR-Ab seronegative gMG in part A

3.1.1. Primary Endpoint

- MG-ADL total score change from baseline to day 29 in part A

3.1.2. Key Secondary Endpoints (Hierarchical Testing)

- QMG total score change from baseline to day 29 in part A
- Proportion of participants who are both MG-ADL and QMG responders in part A

3.2. Secondary Objectives and Endpoints (Nonhierarchical Testing)

Objective	Endpoint
• To determine the efficacy of efgartigimod IV compared to placebo, and the long-term efficacy of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Proportion of participants with MSE (defined as an MG-ADL total score of 0 or 1) • Proportion of participants who are MG-ADL responders in part A • Proportion of participants who are QMG responders in part A • Proportion of participants who are early MG-ADL responders in part A • MG-ADL total score actual value and change from baseline over time in part A and part A+B • QMG total score actual value and change from baseline over time in part A and part A+B • MG-QoL15r score change from baseline to day 29 in part A • MG-QoL15r actual values and change from baseline over time in part A and part A+B • EQ-5D-5L VAS actual value and change from baseline over time in part A and part A+B
• To assess the safety and tolerability of efgartigimod IV compared to placebo and the long-term safety and tolerability of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Incidence and severity of AEs and SAEs in part A and part A+B • Clinically relevant changes in laboratory parameters, ECGs, and vital signs in part A and part A+B

Objective	Endpoint
• To assess the PD effect of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Total IgG concentrations actual values and percent changes from baseline over time in part A and part A+B

3.3. Exploratory

Objective	Endpoint
• To determine the efficacy of efgartigimod IV compared to placebo and the long-term efficacy of efgartigimod IV in participants with AChR-Ab seronegative gMG	• AUEC of change from baseline in the MG-ADL total score from day 1 through end of part A • AUEC of change from baseline in QMG from day 1 through end of part A • MGC actual value and change from baseline over time in part A and part A+B • Neuro-QoL Fatigue actual value and change from baseline over time in part A and part A+B • [redacted] • Proportion of participants in each category of PGI-C and PGI-S in part A and part A+B
• To assess the PK of efgartigimod IV compared to placebo in participants with AChR-Ab seronegative gMG in part A	• C_{max} and C_{trough} in part A
• To assess the [redacted]	• [redacted] and [redacted]
• To assess the immunogenicity of efgartigimod IV in participants with AChR-Ab seronegative gMG	• Incidence and prevalence of ADAs against efgartigimod over time in part A and part A+B • Incidence and prevalence of NAb against efgartigimod over time in part A and part A+B
• To assess participant satisfaction with efgartigimod IV treatment in participants with AChR-Ab seronegative gMG	• TSQM-9 domain scores in part A+B

The primary and key secondary estimands are defined in Sections 9.3.2 and 9.3.3.

4. STUDY DESIGN

4.1. Overall Design

This phase 3, multicenter study in adult participants with AChR-Ab seronegative gMG consists of 2 parts: part A is a randomized, double-blinded, placebo-controlled, parallel-group design to evaluate the efficacy and safety of efgartigimod IV, and part B is open-label to enable the collection of additional long-term efficacy, safety, and tolerability data.

Study periods include the following:

- Screening: up to 5 weeks (refer to Section 8.1.1.2)
- Part A (8 weeks total)
  - Composed of a single TP and IP, grouped as a single cycle
  - TP: 3 weeks of once weekly IMP infusions (4 total)
  - IP: 5 weeks follow-up
- Part B (up to 2 years)
  - Composed of TPs and IPs grouped in cycles (Cn=TPn+IPn)
  - C1 and C2: 3-week TP and 4-week IP
  - C3 onward: 3-week TP and IPs each of indeterminant length based on participant clinical status, no shorter than 7 days after the prior cycle's last efgartigimod IV infusion

An MG diagnostic adjudication committee (Section 10.1.6.2) will confirm participant AChR-Ab seronegative gMG diagnosis before randomization. At part A V1 (baseline), approximately 110 participants whose eligibility was confirmed will be stratified by MuSK-Ab status and randomized in a 1:1 ratio to receive either efgartigimod IV 10 mg/kg or placebo.

In part A, IMP will be administered concomitantly with a stable dose of the participant's current gMG therapy. Participants must maintain a stable regimen of concurrent gMG medications throughout part A until the start of C3 in part B. More details are provided in Section 6.9. From part B C3 TP onward, changes to concomitant gMG treatment are permitted.

Although part B is open-label, participants and investigators will remain blinded to treatment assignment throughout the first 2 cycles in part B to ensure part A data are uncompromised for the interim analysis (Section 9.4).

Participants whose dose was interrupted (1 missing dose) in part A can continue in part B if part A was completed. Participants who are missing more than 1 dose of IMP or receive rescue therapy in part A will not be permitted to transition to part B. Information on participant discontinuation from IMP and withdrawal from study is provided in Section 7.

All participants in part B will receive open-label efgartigimod IV. During part B from C3 onward, TPs can be initiated earlier at the discretion of the investigator.

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

- The participant completed the previous TP
- The participant could benefit from retreatment according to the investigator's judgment
- There is no clinical or laboratory evidence of any concomitant disease that could confound the results of the study or put the participant at undue risk (eg, infection), according to the investigator's judgment
- At least 7 days has elapsed between treatment periods (ie, between the last dose of the previous TP [Cn] and the first dose of the next TP [Cn+1]).
- There must be at least 4 weeks left in the study for the participant, so that a full TP and the EoS visit can be performed.

Part B will remain open in all countries for a maximum of 2 years following completion of part A. Part B may end earlier than 2 years in countries where efgartigimod becomes available for AChR-Ab seronegative gMG commercially or through a continued access program, whichever comes first.

The IDMC will also review and evaluate study data periodically for participant safety, study conduct and progress, and provide recommendations to the sponsor regarding the continuation, modification, or termination of the study.

4.2. Scientific Rationale for Study Design

The inclusion of a placebo control arm in part A of the study allows for an accurate assessment of the safety, tolerability, and efficacy of efgartigimod IV in participants with AChR-Ab seronegative MG. Comparing efgartigimod IV with placebo optimizes the interpretability of the data obtained in the study. To ensure concomitant gMG medications do not impact efficacy measurements, all such therapy must be stable before and during screening (per IC8) and throughout part A until the start of C3 in part B.

The open-label design of part B will allow the collection of efficacy and safety data in the study population to assess efgartigimod IV as an ongoing, long-term maintenance therapy option.

The MG-specific efficacy scales were chosen because they are standardized assessments used to evaluate MG symptoms or MG-related QoL in adults in clinical studies.[31,32] Serial measurements of these assessments while receiving IMP will provide information on the efficacy of efgartigimod compared to placebo in AChR-Ab seronegative participants with gMG.

The EQ-5D-5L is a standardized test recognized by many health authorities as a generic measure of health status for clinical and economical appraisal.

As is recommended for studies involving a biological product for a neurological indication, a prospective assessment for SIB was included in this clinical study. The question from the PHQ-9 was chosen based on its linear relationship between the item 9 score of the PHQ-9 and the risk of subsequent suicide attempt.[33]

4.3. Justification for Dose

The favorable benefit-risk profile of efgartigimod IV 10 mg/kg IV has been well-established in the postmarketing setting and clinical studies conducted to date. This dose achieved near-maximal total IgG reduction, resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in participants with gMG.

4.4. End-of-the-Study Definition

The end of the study is defined as the date of the last participant's last visit. No SFV is required after the EoS (refer to Section 7.1.1).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Is at least 18 years of age and the local legal age of consent for clinical studies when signing the ICF
2. Is capable of providing signed informed consent, as described in Section 10.1.3, and complying with protocol requirements
3. Agrees to use contraceptive measures consistent with local regulations; WOCBP (defined in Section 10.4.1) must have a negative serum pregnancy test result at screening and a negative urine pregnancy test result at baseline before receiving IMP (Section 10.4.2.1)
4. Has no known weakness in infancy and later develop fatigable weakness after aged 16 years and diagnosed with acquired gMG confirmed by documentation (Section 8.1) of both of the following:
    a. History of abnormal neuromuscular transmission demonstrated by single fiber electromyography or RNS or is MuSK-Ab seropositive
    b. Either a history of positive edrophonium chloride test OR a demonstrated improvement in MG signs with treatments such as oral AChE inhibitors, PLEX, immunoabsorption, or IVIg/SCIg treatment
5. Is AChR-Ab seronegative at screening
6. Is MGFA Class II, III, or IV
7. Has a screening and baseline MG-ADL total score ≥5 points with >50% of the score attributed to nonocular symptoms
8. Is receiving a stable dose of MG therapy before screening that includes AChE inhibitors, steroids, or NSISTs in combination or alone, with the following dose conditions:
    a. Nonsteroidal immunosuppressive drugs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide) initiated at least 6 months before screening with no change in dose during the 3 months before screening
    b. Steroids initiated at least 3 months before screening, with no change in dose during the month before screening
    c. AChE inhibitors with no change in dose during the 2 weeks before screening

5.2. Exclusion Criteria

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

1. Known autoimmune disease or any medical condition that would interfere with an accurate assessment of clinical symptoms of gMG or puts the participant at undue risk

2. History of malignancy unless considered cured by adequate treatment with no evidence of recurrence for ≥3 years before first IMP administration. Adequately treated participants with the following cancers can be included at any time:
   - Basal cell or squamous cell skin cancer
   - Carcinoma in situ of the cervix
   - Carcinoma in situ of the breast
   - Incidental histological findings of prostate cancer (TNM stage T1a or T1b)
3. Clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion
4. Positive serum test at screening for active infection with any of the following:
   - HBV indicative of an acute or chronic infection, unless associated with a negative HBV DNA test
   - HCV based on HCV antibody assay unless a negative RNA test is available
   - HIV based on test results of a CD4 count <200 cells/mm^3 and associated with an AIDS-defining condition
   - HIV based on test results of a CD4 count ≥200 cells/mm^3 but not adequately treated with antiviral therapy
5. Clinically significant disease, recent major surgery (within 3 months of screening), or intention to have major surgery during the study; or any other medical condition that, in the investigator's opinion, would confound the results of the study or put the participant at undue risk
6. Current participation in another interventional clinical study
7. Known hypersensitivity to IMP or any of its excipients
8. History (within 12 months before screening) of or current alcohol, drug, or medication abuse as assessed by the investigator
9. Pregnant or lactating state or intention to become pregnant during the study
10. Total IgG <4 g/L at screening
11. Severe renal impairment with eGFR <30 mL/min/1.7.3 m^2 at screening
12. Live or live-attenuated vaccine received less than 4 weeks before screening
13. Previous participation in an efgartigimod clinical study and received at least 1 dose of IMP
14. Worsening muscle weakness secondary to concurrent infections or medications (eg, aminoglycosides, beta-blockers)
15. Documented lack of clinical response to PLEX
16. Received a thymectomy less than 3 months before screening or thymectomy is planned during the study

17. Using the following prior or concomitant therapies:
    a. Any other IMP received less than 3 months or 5 half-lives (whichever is longer) before this study's first IMP dose
    b. Any monoclonal antibody received less than 6 months before the first IMP dose, except eculizumab, which is less than 3 months before the first IMP dose
    c. IVIg, SCIg, or intramuscular Ig received less than 4 weeks before baseline
    d. PLEX received less than 4 weeks before baseline
    e. Anti-CD20 or anti-CD-19 antibody received less than 6 months before screening
    f. Prior treatment with any form of CAR T-cell therapy or IL-6(R) inhibitor
    g. Previously received at least 1 administration of efgartigimod or another FcRn inhibitor
18. The participant has any relationship of dependency with the sponsor.

5.3. Lifestyle Considerations

There are no lifestyle considerations for this study.

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, SAE reports) is required to ensure transparent reporting of screen failure participants and address regulatory authority queries.

- Retesting: Participants with exclusionary clinical laboratory results, ECGs, vital sign measurements, etc that are inconsistent with their medical history or clinical evaluation, can be retested once within the remaining screening period to confirm the test value(s).
  - Participants receiving rescue therapy (Section 6.9.1) during screening may be retested for eligibility after the 4-week washout period. From the screening activities, only clinical laboratory testing, including urinalysis, must be repeated. Participants without clinically significant test findings may attend the baseline visit with rescreening.
- Rescreening: Participants who do not initially meet this study's eligibility criteria can be rescreened once. For example, a participant who does not meet eligibility criteria because of an acute illness ongoing during screening (considering the illness itself does not violate inclusion/exclusion criteria), they can be rescreened once the illness is resolved, or the medical issue stabilized. Rescreened participants will be reconsented and assigned a new participant number for each rescreening event.

5.5. Criteria for Temporarily Delaying IMP Administration

Delaying (or interrupting) administration of the IMP must occur if the investigator considers it in the best interest of the participant. If the IMP cannot be administered within the specified time window (Table 1 and Table 2), that IMP dose will be missed (Section 7.1.2).

6. STUDY DRUG(S) AND CONCOMITANT THERAPY

All IMP is manufactured according to Good Manufacturing Practice regulations.

6.1. Investigational Medicinal Product Administered

IMP is described in Table 4.

Table 4: IMP(s) Administered

IMP label	Efgartigimod IV	Placebo IV
IMP name	Efgartigimod formulation for IV infusion	Placebo solution for IV infusion
IMP description	IV, 10 mg/kg, 1-hour infusion	IV, 1-hour infusion
Type	Biologic	Placebo
Dose formulation	Infusion	Infusion
Unit dose strength(s)	20 mg/mL	Not applicable
Dosage level(s)	4 infusions over 3 weeks per TP	4 infusions over 3 weeks
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Centrally by the sponsor	Centrally by the sponsor
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled per country requirements	IMP will be provided in glass vials. Each vial will be labeled per country requirements
Former name	ARGX-113	Not applicable

AxMP=auxiliary medicinal product; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product; TP=treatment period

Table 5: Study Arms/Groups

	Part A		**Part B**
Arm/group title	**Efgartigimod IV**	**Placebo**	**Efgartigimod IV**
Arm/group type	Experimental	Placebo comparator	Experimental
Arm/group description	Infusions of efgartigimod IV 10 mg/mL once weekly for 3 weeks (4 infusions total) per TP, followed by a 5-week follow-up period	Infusions of placebo once weekly for 3 weeks (4 infusions total) per TP, followed by a 5-week follow-up period	C1 and C2 efgartigimod IV 10 mg/mL once weekly for 3 weeks (4 infusions total) per TP, followed by a 4-week IP From C3 onward, the duration of each IP will depend on the participant's clinical status, no shorter than 7 days The number and frequency of cycles will vary for up to 2 years
Associated IMP labels	Efgartigimod IV	Placebo IV	Efgartigimod IV

Cn=cycle number; efgartigimod IV=efgartigimod for IV administration; IMP=investigational medicinal product; IP=intertreatment period; IV=intravenous(ly); TP=treatment period

6.2. Preparation, Handling, Storage, and Accountability

- The IMP will be supplied to the investigational site by the sponsor's designated IMP supply vendor.
- The IP handling manual provides instructions on preparing, handling, storing, disposing, and the accountability of IMP.
- The investigator or designee is responsible for the correct and safe storage of IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area following the labeled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMP received during transit. Any discrepancies are reported and resolved before using the IMP.
- Only participants enrolled in the study are permitted to receive IMP, and only authorized site staff or designee are allowed to supply IMP.

- Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared before administration with an IV pump.
- IMP must be stored refrigerated (2 °C to 8 °C) and protected from direct sunlight in secondary packaging. Do not shake IMP or expose it to freezing temperatures.
- Participants will be observed for at least 30 minutes after the end of IMP infusion for routine safety monitoring.

6.3. Assignment to IMP

- In part A, at V1 and once eligibility has been confirmed, participants will be stratified by MuSK-Ab status and randomized in 1:1 ratio to receive placebo or efgartigimod IV.
- In part B, all participants will be assigned to receive efgartigimod IV.

6.4. Blinding

Part A is double-blinded. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator is solely responsible for determining if unblinding of the IMP assignment is necessary. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator can contact the sponsor before unblinding a participant's IMP unless this could delay emergency treatment for the participant. If a participant's IMP assignment has been unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the source documents. Refer to Section 9.4.

Part B is open-label.

6.5. Study Compliance

Participants will receive IMP under medical supervision at the site. The date and time of each dose administered will be recorded in the source documents.

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 ±10% during the study.

6.7. Continued Access to Efgartigimod 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 IV greater than 10% of the planned dosage amount within a single infusion will be considered a protocol-defined 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. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements [including Chinese traditional medicine]) or other specific categories of interest that the participant is receiving at the time of screening or receives during the study must be recorded and include the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information (ie, dose and frequency)

Prohibited prior and concomitant medications are listed in EC17.

Instructions for the appropriate administration of live and live-attenuate vaccines are provided in the efgartigimod IB.

Participants must maintain a stable regimen of gMG medications before and during screening (per IC8) and throughout part A until the start of C3 in part B. Changes to concomitant gMG treatment are generally unrestricted from C3 in part B onward. (Section 6.9.1 describes restrictions related to rescue medication.)

AChE inhibitors must be withheld for at least 12 hours before assessing QMG (Section 8.2.2). Complying with this requirement is not considered a change in the participant's concomitant gMG treatment.

6.9.1. Rescue Medication

PLEX, IVIg/SCIg, immunoadsorption, or an increase in dosage or type of corticosteroid are considered rescue therapy when both of the following conditions apply:

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

Recorded in the source documents will be the date and time of rescue medication administration, with the name, dosage regimen, and response to the rescue medication.

Participants in part A who receive rescue therapy under the aforementioned conditions will be permanently discontinued from the study and ineligible for part B (refer to Section 7). Participants in part B who receive rescue therapy under the aforementioned conditions will not be discontinued from the study unless rescue therapy is administered in response to a life-threatening situation. Participants may not receive PLEX, Ig therapy, or immunoadsorption more than 3 times per calendar year in part B.

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Information on discontinuation of specific sites or the entire study is provided 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. A participant will not be automatically withdrawn from the study if IMP treatment is discontinued before the end of the study.

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

Participants who permanently discontinue IMP will be encouraged to remain in the study and attend any previously scheduled visits in part A, even if only by telephone. Participants unwilling to travel to on-site visits for AE and concomitant medication monitoring will be offered the option to attend these visits by web teleconferencing or telephone. If the participant cannot attend the previously scheduled visits for any reason, the study site will minimally perform the EDV and the SFV on-site.

Unless consent from the study has been withdrawn, the participant will attend an EDV and an SFV. Study sites will attempt to perform the EDV within 7 days after the participant's final IMP administration. If IMP is discontinued early, a SFV will occur 56 (±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 8.3.5).
- 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 IMP.
- Participant receives a prohibited medication or substance (Section 6.9).
- Participant receives rescue medication or misses more than 1 dose of IMP in part A (Section 6.9.1).
- Participant receives rescue therapy more than 3 times in a single calendar year in part B.

Participants permanently discontinuing IMP in part A will be ineligible to continue in part B.

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

One missed dose in part A is permitted as a temporary discontinuation (Section 7.1.1).

Temporary discontinuation of IMP will also occur if the participant's treatment allocation becomes unblinded during part A, in which case the participant can resume IMP at the start of part B.

7.2. Participant Discontinuation/Withdrawal From the Study

Study withdrawal is defined as the permanent cessation of further participation in any study assessment before its planned completion.

The primary reason for permanent study withdrawal will be recorded.

The following circumstances will result in permanent discontinuation of IMP and withdrawal from the study:

- Participant withdrawal of consent
- Sponsor request (eg, following IDMC advice)

If the participant withdraws consent to participate in the study, the sponsor can retain and continue to use any data collected before such consent was withdrawn. Future research on samples collected before withdrawal of consent will not be impacted unless the participant has also withdrawn consent for future research.

7.3. Lost to Follow-up

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

The following actions must be completed if a participant fails to complete 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 continue in the study.
- Before a participant is considered lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (when possible, 3 phone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's source documentation.

- Participants who continue to be unreachable will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Protocol waivers or exemptions are not allowed.
- Participants are enrolled in the study once the informed consent form has been signed.
- Adherence to the study design requirements, including those specified in the SoA, is required for study conduct.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Instructions on completing some of these assessments are provided in the study manual.
- 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 confirm eligibility or record reasons for screening failure, as applicable.
- Operational considerations related to the COVID-19 pandemic are provided in Section 10.5

8.1. Administrative and General/Baseline Procedures

All significant findings, surgeries, and preexisting conditions (including allergies, if any) present at screening will be reported. Complete information will be collected on medical and surgical history and concomitant medical conditions, specifying those ongoing at screening.

Scenarios that could result in a prolongation of the up to 5-week screening period are described in Section 5.4 and Section 8.1.1.

8.1.1. MG Diagnostic Considerations

8.1.1.1. Diagnostic Testing

During the screening period, the diagnosis of AChR-Ab seronegative gMG will be confirmed by an MG diagnostic adjudication committee. Additional assessments that are not listed in the SoA may be requested during the screening period to support the confirmation of AChR-Ab seronegative gMG diagnosis.

8.1.1.2. MG Diagnostic Adjudication Committee

Documentation of MG diagnosis for IC4 and response to MG treatment will be reviewed by a panel of experts (Section 10.1.6.2). Sites are expected to submit anonymized SFEMG or RNS test results, edrophonium chloride test results, and documentation of response to gMG treatment. The MG diagnostic adjudication committee may request an extension of the screening period for up to 1 week.

8.1.2. Use and Storage of Biological Samples

Biological samples collected at screening can be used to validate methods to measure antibodies, biomarkers, and efgartigimod serum concentrations. Participants must consent to their samples being used in this manner before such measurements are made.

After the protocol-defined laboratory analyses have been completed, any samples remaining can be stored for up to 15 years after the end of the study, in the laboratory or long-term storage designated by the sponsor or research partners worldwide. These samples may be used for future additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or gMG, unless prohibited by local regulations or the participant.

8.2. Efficacy Assessments

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

Instructions on how to complete these assessments are provided in the study manual.

8.2.1. MG-ADL

The MG-ADL scale is an 8-item instrument used to assess MG symptoms and their effects on daily activities. The scale comprises 2 items on daily life activities and 6 items on symptoms. The daily living items are (1) ability to brush teeth or comb hair and (2) limitations in the ability to rise from a chair. The 6 MG symptom categories are the following:

diplopia	chewing	voice/speech
ptosis	swallowing	respiratory

Each item is graded on 4-point symptom severity scale (0=normal to 3=most severe), with the total score ranging from 0 to 24. The MG-ADL will be assessed and scored by a trained and certified evaluator.

A CMI on the MG-ADL is defined as a ≥2-point reduction in score[34,35] and MSE is a score of 0 or 1.[35]

8.2.2. QMG

The QMG quantifies disease severity based on impairments of body functions and structures, as defined by the International Classification of Functioning, Disability, and Health.[36] The QMG includes 13 items that measure endurance or fatigability and accounts for fluctuations in disease state.

Test domains are as follows:

- Ocular function (3 items)
- Oropharyngeal/respiratory function (3 items)
- Axial/limb function (7 items)

Each item will be scored on a 4-point severity scale (0=no symptoms to 3=severe symptoms). Permissible scores range from 0 to 39, with higher scores indicative of greater disease severity. The QMG will be assessed and scored by a trained and certified evaluator.

Participants receiving AChE inhibitors will refrain from any dose during the 12-hour period before the scheduled QMG assessment. The date and time of last AChE inhibitor dose will be recorded in the source documents.

Whenever possible, the QMG assessment will occur during the morning. If the morning assessment is not feasible, each QMG assessment will be performed at the same time of day.

A CMI on the QMG scale is defined as a ≥3-point reduction in score.[37]

8.2.3. MGC

The MGC is a composite of 10 items combining a trained evaluator's examination and patient-reported outcomes. Items were selected based on responsiveness to treatment (defined by a positive physicians' and patients' impression of change), and correlations with the MG-QoL15.[38] There are 6 items evaluated by a trained rater, including ptosis, double vision, eye closure, neck flexion, shoulder abduction, and hip flexion. The 4 items on bulbar function (ie, talking, chewing, swallowing, and breathing) are reported by the participant and derived from the MG-ADL.

Items are scored on a 4-point severity scale with higher scores indicating more severe symptoms. Scores on items related to bulbar impairment are weighted more heavily than scores on ocular items. The total MGC score ranges from 0 (no symptoms) to 50 (maximum severity).

A CMI on the MGC is defined as a 3-point reduction in score.[39]

8.2.4. [redacted]

The [redacted][31] includes both [redacted] and [redacted] that measure [redacted] It comprises [redacted] with [redacted] reflecting [redacted] Total scores for the [redacted] can range from [redacted], and higher scores represent [redacted]

8.2.5. MG-QoL15r

The MG-QoL15r[40] questionnaire (a revised version of the MG-QoL15) is a patient-reported instrument that measures the impact of MG symptoms on QoL. The scale includes 15 items that assess ocular symptoms, swallowing, speech, proximal limb function, mobility, personal grooming, work, social life, activities, fluctuations, and psychological items. Scoring is qualitative with each item having 3 response options: 0 (not at all), 1 (somewhat), and 2 (very much); total scores range from 0 to 30. A higher score indicates lesser QoL.

8.2.6. Neuro-QoL Short Form – Fatigue

The Neuro-QoL Fatigue Scale[41,42] is a patient-reported outcome measuring feelings of fatigue for use in neurological diseases. The Neuro-QoL Fatigue 8-item short form questionnaire measures sensations ranging from "tiredness" to an "overwhelming, debilitating, and sustained sense of exhaustion" that negatively impact a respondent's ability to perform normal activities. Each item is scored from 1 (never) to 5 (always). Total scores range from 8 to 40; higher scores indicate greater fatigue.

8.2.7. PGI

The PGI-S and PGI-C questionnaires[43] are simple, valid, participant-rated, assessments of perceived severity of overall status and change, respectively.

- PGI-S is graded on a 5-point Likert scale with scores ranging from 1 (none) to 5 (very severe).

- PGI-C is graded on a 7-point Likert scale with scores ranging from 1 (very much improved) to 7 (very much worse).

8.2.8. EQ-5D-5L

The EQ-5D-5L is a participant-reported measure of health status developed by the EuroQol Group.[44] The questionnaire comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Current health is rated for each dimension on a 5-item Likert scale ranging from 1 (no problem) to 5 (extreme problem). Additionally, current health status is rated on vertical VAS from 0 to 100, with a score of 0 corresponding to "the worst health you can imagine" and 100 corresponding to "the best health you can imagine."

8.2.9. TSQM-9

The TSQM-9[45] is a 9-item validated instrument comprising 3 domains: effectiveness (3 questions), convenience (3 questions), and global satisfaction (3 questions).

Likert scales of either 7 or 5 points are used and domain scores range from 0 to 100, with higher scores representing higher satisfaction in that domain.

8.3. Safety Assessments

Time points 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 that confirms a pre-existing condition will be reported as medical history. After signing the informed consent, any new abnormal or worsened pre-existing condition the investigator considers clinically significant will be reported as an AE.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the musculoskeletal, gastrointestinal, pulmonary, cardiovascular, respiratory, and neurological systems and general appearance, skin, and lymph nodes. Height and weight will also be measured without shoes, attired in light clothing, and recorded using calibrated instruments.
- A brief physical examination will include assessments of gastrointestinal, pulmonary, cardiovascular, and respiratory systems and general appearance.

8.3.2. Vital Sign Measurements

- Body temperature, pulse rate, and blood pressure will be recorded before blood collection for laboratory tests.
- Blood pressure and pulse will be assessed with the participant rested and seated for at least 5 minutes.

8.3.3. Electrocardiograms

- A single 12-lead (or higher, according to local requirements) ECG will be obtained using an ECG machine that calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

8.3.4. Protocol-Required Laboratory Tests

- Refer to Appendix 2 (Table 7) for the list of protocol-required laboratory tests to be performed and the SoA (Section 1.3) for the timing.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- Blood and urine samples will be analyzed at a central laboratory for serum chemistry and hematology, urinalysis, serology (eg, viral marker testing), and specialty laboratory parameters (sample processing country-specific differences are provided in Section 10.8).

8.3.5. Pregnancy Testing

- WOCBP will be tested for pregnancy by serum at screening. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3).
- Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFV).
- Additional pregnancy testing may be performed as necessary by the investigator or as required by local regulations, to establish the absence of pregnancy at any time during the study.
- Any pregnancy reported during a clinical research study, including the safety follow-up period, is routinely monitored as standard practice. The pregnancy could have arisen from a female clinical study participant or a male participant's female partner. In either situation, consent will be requested to collect medical information about the pregnancy and the baby's health for up to12 months after the baby's birth.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Patients with gMG can occasionally develop suicidal ideation.

Participants will be monitored appropriately for SIB or any other unusual changes in behavior throughout the study. Baseline assessment of SIB/treatment-emergent SIB will be monitored during this study using the PHQ-9. Participants who show symptoms of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AE and SAE are provided in Appendix 3 (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 8.4.6.

AEs (including SAEs, AESIs, and AEs of clinical interest) will be reported by the participant (or, if appropriate, by the caregiver or surrogate).

The investigator and qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and monitoring all reported events, including those reported by the participant.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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

All AEs will be collected from the signing of the ICF until the SFV, as specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately, and under no circumstance will this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator must proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs defined in Section 8.4.6 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of IMP 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 IMP 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 SAE listing) from the sponsor will review and file it with the IB and notify the IRB/IEC, if appropriate, according to local requirements.
- The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities via the appropriate reporting systems (eg, Eudravigilance and FDA AE reporting system), per applicable regulatory requirements. The sponsor or designee will also be responsible for forwarding SUSAR reports to all study investigators, who will be required to report these SUSARs to their respective IECs/IRBs per local regulatory requirements.

8.4.5. Pregnancy

- If pregnancy is reported, the investigator will record the pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy in the female participant or the female partner of the male participant. Contact details are provided in Serious Adverse Event Reporting.
- The participant and pregnant female partner, if consented (Section 10.1.3), will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and forward it to the sponsor.
- While pregnancy itself is not considered 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 accordingly.
- Any poststudy pregnancy-related SAE considered reasonably related by the investigator to IMP will be reported to the sponsor as described in Section 8.4.4.
- Any female participant who becomes pregnant during the study will discontinue IMP.

8.4.6. AESIs

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program. An AESI can be serious or nonserious, related or not related to the IMP or study procedures. These events will be reported according to the same time frame as that for SAEs specified in Section 8.4.1 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. These events will be reported according to the time frame specified in Section 8.4.1 and Section 10.3.4, with the following information provided:

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

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

8.4.7. AEs of Clinical Interest

8.4.7.1. 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 administration, injection- or infusion-related reactions can occur during or after administration.

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

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

8.5. Pharmacokinetics

Blood samples for PK analysis will be collected predose on IMP administration visits (within 2 hours before IMP administration) and 1 postdose (within 1 hour after the end of the infusion) as described in the SoA (Section 1.3).

Efgartigimod serum concentrations will be determined using validated methods.

8.6. Pharmacodynamics

Baseline and postbaseline PD blood samples will be collected predose on IMP administration visits (within 2 hours before IMP administration) as described in the SoA (Section 1.3).

Total IgG levels will be quantified at a central laboratory using a validated method. [redacted] and [redacted]

Total IgG [redacted] results will not be reported to investigative sites or other site staff to maintain study blind.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Blood samples (serum, plasma and whole blood for PBMCs) will be collected at the time points provided in the SoA (Section 1.3) from all participants who have provided separate consent for biomarker analysis.

Blood samples may also be used to cross-validate the biomarker assays in MG matrix (serum/plasma).

Biomarkers will be analyzed and reported separately from the main CSR. Sample processing country-specific differences are provided in Section 10.8.

8.9. Immunogenicity Assessments

Blood samples will be collected to assess the serum levels of ADAs and presence of NAb against efgartigimod from all participants as indicated in the SoA (Section 1.3). Samples will be collected predose on IMP administration visits (within ≤ 2 hours before IMP administration).

Samples will be analyzed by the designated laboratory in a tiered approach using validated immunogenicity assays.[46]

8.10. Health Economics

Medical resource and health-economic parameters including ER visits, hospitalizations, and ICU admissions will be recorded to assess any changes in these parameters with IMP administration. Historical data on these parameters from at least 12 months before starting the study will be collected at the start of the study, if available.

9. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by the sponsor's designated CRO using 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 specified.

A detailed and comprehensive SAP will be written and approved before interim/final analysis database lock. Minor changes to the statistical methods set out in this protocol do not require a protocol amendment but will be documented (as changes from the protocol) in the SAP and in the study report(s). The following paragraphs contain the main general features of the statistical analyses. Additional details will be provided as needed in the SAP.

9.1. Statistical Hypotheses

The statistical hypothesis is derived from the primary study objective as stated in Section 3.

The primary endpoint in this study is the change from baseline in MG-ADL total score at day 29 (week 4). The primary hypothesis tested in the study is the following:

$$H_0: \delta\ \Delta\mu_{EFG} - \Delta\mu_{PBO}=0$$

$$H_1: \delta=\Delta\mu_{EFG} - \Delta\mu_{PBO}\neq 0$$

$\Delta\mu_{EFG}$ is the mean change from baseline in MG-ADL total score at day 29 (week 4) in the efgartigimod IV arm and $\Delta\mu_{PBO}$ is the mean change from baseline in MG-ADL total score at day 29 (week 4) in the placebo arm.

- Null hypothesis: no difference between efgartigimod IV and placebo in mean change from baseline in MG-ADL total scores at day 29 (week 4)
- Alternative hypothesis: difference between efgartigimod IV and placebo in mean change from baseline in MG-ADL total scores at day 29 (week 4)

The null and alternative hypotheses corresponding to the secondary estimands (hierarchical testing, refer to Section 9.1.1) are as follows:

- Secondary objective [1]:
  - Null hypothesis: no difference between efgartigimod IV and placebo in mean change from baseline in QMG total scores at day 29 (week 4)
  - Alternative hypothesis: difference between efgartigimod IV and placebo in mean change from baseline in QMG total scores at day 29 (week 4)
- Secondary objective [2]:
  - Null hypothesis: no difference between efgartigimod IV and placebo in achieving both MG-ADL and QMG responder status
  - Alternative hypothesis: difference between efgartigimod IV and placebo in achieving both MG-ADL and QMG responder status

9.1.1. Multiplicity Adjustment

Given the cumulative efficacy data of efgartigimod in AChR-Ab seronegative patients with gMG and the fact that the study includes a rare subset of an already rare disease, a closed testing procedure that controls the family-wise error rate in the strong sense at the overall [redacted]% level will be applied.

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoints will be conducted in the hierarchical order as indicated in Section 3.1. This means the statistical hypotheses are tested in the prespecified order at the same significance level of α=10% using 2-sided tests if all preceding hypotheses are rejected. Once a hypothesis is not rejected, subsequent hypotheses cannot be formally tested and therefore cannot be rejected.

9.2. Analysis Sets

The following participant analysis sets are defined:

Analysis set	Description
Enrolled analysis set	All participants who provided informed consent
ITT analysis set	All randomized participants
Safety analysis set (part A)	All participants who received at least 1 IMP dose or part of a dose in part A
Safety analysis set (part A+B)	All participants who received at least 1 dose of efgartigimod IV or part of a dose in part A or B
PK analysis set (part A)	All participants in the safety analysis set (part A) for whom at least 1 postdose serum PK concentration is available in part A, excluding participants in the placebo arm

When using the ITT analysis set, participants will be classified according to their planned treatment arm. For analyses performed on the safety or PK analysis set, the actual treatment arm will be considered. The actual treatment arm will be the same as the planned treatment arm unless the participant received IMP other than that planned for the study.

9.3. Statistical Analyses

9.3.1. General Considerations

The following 3 baseline types will be defined:

- The **study baseline** value (part A) is defined as the last available nonmissing value before the first administration of IMP.
- The **pooled baseline** values (part A+B) are defined as the last available nonmissing value before the first administration of efgartigimod IV. For participants in the efgartigimod IV arm, this will align with the study baseline. For participants in the placebo arm, this will align with the last available nonmissing value before the first administration in part B.
- The **cycle n baseline** value (part A+B) is defined as the last available nonmissing value before the first administration of IMP in cycle n.

All study visits will be recalculated based on actual dates and referred to as "analysis visits," which will be used in the statistical analyses. The rules for calculating the analysis visits will be documented in the SAP.

Summary tables will summarize endpoints by part A and part A+B, where applicable. Summary tables related to part A will be presented by treatment arm and analysis visit, while summary tables related to part A+B will be presented by cycle and overall, in the following subgroups:

- EFG-EFG: participants in the efgartigimod IV arm who received efgartigimod IV in part A and/or B. Data related to part A and part B will be considered for this subgroup.
- PBO-EFG: participants in the placebo arm who received efgartigimod IV in part B. Only data related to part B will be considered for this subgroup.
- Total EFG: participants in the EFG-EFG and PBO-EFG groups.

The total group will be the focus analysis in part A+B, unless otherwise specified.

The number of participants will differ across cycles because of the difference in length of the observational periods in part A+B. The number of participants in the first cycle will be higher than the number of participants in the second cycle and so forth. To account for this attrition, cohorts of participants with at least 2 cycles, with at least 3 cycles, at least n cycles will be created. The analyses performed on the safety analysis set using all available data will be repeated for each of these cohorts to evaluate long-term safety over cycles within similar cohorts. A cohort will need to contain at least 10 participants to be shown in the results (eg, if the total number of participants with at least 6 cycles is fewer than 10, data for this cohort will not be presented in the tables).

Descriptive statistics for continuous variables, will include the number of participants (with nonmissing values), arithmetic mean, SD, median, quartiles, minimum, and maximum will be presented. For efficacy and PD measures, the SE and 95% CI will also be provided in the descriptive statistics. Descriptive statistics for PK serum concentrations will include the number of observed values, arithmetic mean, SD, median, minimum and maximum, CV%, the GM, and geometric CV%. Serum concentrations will be reported as received by the bioanalytical laboratory. Descriptive statistics for immunogenicity titer values will include the number of observed values, arithmetic mean, SE, 95% CI, median, Q1, Q3, minimum, maximum, the GM, and geometric CV%.

For categorical variables, the number and percentage of participants will be shown using frequency and cross-tabulations, as appropriate. Missing values will not be included in the denominator count when computing percentages. For cross-tabulation of postbaseline results versus baseline results, a "missing" category will be shown for baseline results, if applicable.

All efficacy analyses will be performed in the ITT analysis set. All safety analyses, PD, and immunogenicity will be performed in the safety analysis set. The PK analysis set will be used for the PK analysis.

Additional details on the planned analyses and endpoints will be provided in the SAP.

9.3.2. Primary Estimand Analysis

9.3.2.1. Definition of Endpoint

The primary clinical question of interest is the following:

> What is the difference in mean changes from baseline in MG-ADL total score at day 29 (week 4) in participants with AChR-Ab seronegative gMG administered efgartigimod IV vs placebo?

The following attributes describe the estimand:

- Population: adult patients with AChR-Ab seronegative gMG
- Endpoint: change from baseline at day 29 (ie, 7 days after the fourth IMP administration; week 4) in the MG-ADL total score
- Treatment condition: IMP (efgartigimod IV vs placebo)
- ICEs:

ICE	Strategy
• Initiating rescue therapy (Section 6.9.1) before day 29 (week 4)	**Treatment policy**: the occurrence of the ICE is considered irrelevant, and all data are taken as collected.
• Discontinuing IMP for any reason	**Treatment policy**: the occurrence of the ICE is considered irrelevant, and all data are taken as collected.

- Population-level summary: the difference in mean changes between treatment conditions

9.3.2.2. Main Analytical Approach

The hypothesis to be tested is described in Section 9.1. An MMRM approach will be used to model the changes from baseline in the MG-ADL total score at week 1 through week 4 while assuming an unstructured variance-covariance structure for the repeated measures from a participant. The model will include the baseline MG-ADL total score as a covariate, visit and treatment arm as factors, and the interaction term between treatment arm and visit. The least square mean estimate for the mean difference between the 2 treatment arms at the week 4 visit and its associated 2-sided 90% CI, and the p-value for testing the primary hypothesis as stated in the sample size calculation section will be presented. In addition, the least square mean estimate for the mean change from baseline in the MG-ADL total score at week 4 visit and its associated 2-sided 95% CI will be presented for each treatment arm. The Kenward-Roger approach will be used to estimate the denominator degrees of freedom.

After handling ICEs as described above, all randomized participants with both a baseline MG-ADL total score and ≥1 postbaseline MG-ADL total score at or before the week 4 visit will be included in the MMRM.

9.3.2.3. Sensitivity Analysis

Additional sensitivity analyses may be considered with details provided in the SAP.

9.3.2.4. Supplementary Analysis

Instead of using a treatment policy strategy to handle the ICE related to initiation of a rescue therapy before week 4, the main analytical approach will be repeated using a hypothetical strategy instead. The MG-ADL total score after the ICE will be censored and imputed under the hypothetical condition in which rescue therapy was not administered, per maximum likelihood method underlying the MMRM.

Additional supplementary analyses may be considered with details provided in the SAP.

9.3.3. Key Secondary Estimands and Secondary Endpoints Analysis

9.3.3.1. Definition of Endpoints

The clinical questions of interest for the key secondary objectives are the following:

- What is the difference in mean changes from baseline in QMG total score at day 29 (week 4) in participants with AChR-Ab seronegative gMG administered efgartigimod IV vs placebo?
- What is the difference in the proportion of participants with AChR-Ab seronegative gMG achieving both MG-ADL and QMG responder status administered efgartigimod IV vs placebo?

The following attributes describe the estimands:

- Population: same as that described for the primary estimand
- Endpoints:
  - Change from baseline at day 29 (ie, 7 days after the fourth IMP administration; week 4) in QMG total score
  - Achievement of (a) a reduction of ≥2 points from baseline in the MG-ADL total score for ≥4 consecutive weeks with the first reduction occurring no later than 1 week after last IMP administration (ie, an MG-ADL responder), and (b) a reduction of ≥3 points from baseline in the QMG score for ≥4 consecutive weeks with the first reduction occurring no later than 1 week after last IMP administration (ie, a QMG responder)
- Treatment condition: IMP (efgartigimod IV compared with placebo)

- ICEs:

ICE	Strategy
• Initiating rescue therapy (Section 6.9.1) before day 29 (week 4)	**Treatment policy (continuous endpoint)**: the occurrence of the ICE is considered irrelevant, and all data are taken as collected.
• Initiating rescue therapy (Section 6.9.1)	**Composite (categorical endpoint):** participant will be classified as a failure (nonresponder) if responder status was not achieved before the ICE.
• Discontinuing IMP	**Treatment policy**: the occurrence of the ICE is considered irrelevant, and all data are taken as collected.

- Population-level summary:
  - The difference in mean changes between treatment conditions
  - The difference in the proportion of participants with response

No estimands will be defined for the other secondary endpoints, which include the difference in mean changes from baseline in the MG-QoL15r score at day 29 (week 4) between treatment arms, the actual values and changes from baseline in MG-ADL, QMG, MG-QoL15r, and EQ-5D-5L VAS score over time (continuous variables) in part A and part A+B, and the number and percentage of participants achieving MSE in MG-ADL, who are MG-ADL responders, QMG responders or early MG-ADL responders in part A (categorical variables).

9.3.3.2. Analytical Approach

The hypotheses to be tested is described in Section 9.1, including the multiplicity adjustment.

The hierarchical secondary endpoint of change from baseline in the QMG total score at week 4 will be analyzed in a similar approach as the primary analysis of the primary endpoint (Section 9.3.2).

The hierarchical secondary endpoint of response status on both the MG-ADL and QMG scales will be analyzed using the Cochran Mantel-Haenszel statistic. The odds ratio of response rate between the 2 treatment arms and its associated 2-sided 90% CI and the p-value will be presented. Also, an adjusted difference of the proportions with its 90% CI may be provided. In addition, summary statistics including the number of participants and the number and percentage of responders will be presented by treatment arm.

After handling ICEs, as described in Section 9.3.3.1, the following rules will be applied for the handling of missing values in the derivation of response status on the MG-ADL or QMG scales:

- Intermittent missing data at only 1 of 4 postonset (O) consecutive analysis windows: If the missing data follows 1 of the following score patterns: OXmXX, OmXXX, OXXXmX or OXXmX, the participant will be considered as having achieved a response. If no such pattern is present, the participant will be considered not having achieved a response.

- Intermittent missing data following onset of response at ≥2 of 4 consecutive postonset analysis windows: regardless of the reason for missing data, the patient will be considered as not having achieved a sustained response.

Table 6: Handling of Missing Data at ≥1 Consecutive Analysis Windows After Response Onset

Reason for missing data	Score change pattern	Interpretation (binary response)
Missing data at 1 visit after onset of response	OXmXX, OXXmX, OmXXX, or OXXXmX	Responder
	mOXXX or OXXXmY[a]	Nonresponder
Missing data ≥2 or 4 consecutive visits after onset of response	NA	Nonresponder

IMP=investigational medicinal product; m=missing value; MG-ADL=Myasthenia Gravis Activities of Daily Living; NA=not applicable; X=reduction in ≥2 points in the MG-ADL total score or 3 points in the QMG total score; Y=increase or reduction of less than 2 points in the MG-ADL total score or 3 points in the QMG total score

[a] A sequence of nonresponse will be overruled if a participants also fulfills the criteria of being a responder with onset any time at or before 1 week after the last administration of the IMP.

All other secondary endpoints will be summarized with descriptive statistics as described in Section 9.3.1. Frequency tabulations of MG-ADL/QMG actual value and change from baseline over time in part A will also be included with cumulative percentages from worst to best score. Summary tables for the continuous variables in part A will include confidence limits for difference in change based on a two-sample t-test (using Satterthwaite's approximation). Frequency tabulations for the categorical variables will include odds ratio of response rate and differences in odds ratio using the Cochran Mantel-Haenszel statistic. Also, an adjusted difference of the proportions with its 95% CI may be provided.

9.3.3.3. Sensitivity Analysis

Additional sensitivity analyses may be considered with details provided in the SAP.

9.3.3.4. Supplementary Analysis

Instead of using a treatment policy strategy for the continuous endpoint to handle the ICE related to initiation of a rescue therapy before day 29 (week 4), the main analytical approach will be repeated using a hypothetical strategy instead. The QMG total score after the ICE will be censored and imputed under the hypothetical condition in which rescue therapy was not administered, per maximum likelihood method underlying the MMRM.

Additionally, instead of using a composite strategy for the categorical endpoint to handle the ICE related to initiation of a rescue therapy, the main analytical approach will be repeated using a treatment policy strategy. The achievement of both the MG-ADL and QMG responder status will be derived using all data as collected, considering the occurrence of the ICE as irrelevant.

Additional supplementary analyses may be considered. Details will be provided in the SAP.

9.3.4. Exploratory Endpoints Analysis

No estimands will be defined for the exploratory endpoints, which include the difference in AUEC of changes from baseline in MG-ADL and QMG total scores from day 1 through the end of part A between treatment arms, the actual values and changes from baseline in MGC, Neuro-QoL fatigue, and [redacted] in part A and part A+B, and the number and percentage participants in each category of PGI-S and PGI-C (categorical) in part A and part A+B. These endpoints will be summarized with descriptive statistics as described in Section 9.3.1. Summary tables of part A for the continuous variables will include confidence limits for the difference in the change based on a 2-sample t-test (using Satterthwaite's approximation). Frequency tabulations for the categorical variables in part A and part A+B will include cumulative percentages from worst to best category.

9.3.5. Safety Analyses

Incidence and severity of AEs and SAEs and changes in laboratory test results, vital sign measurements, and ECG results will be summarized with descriptive statistics as described in Section 9.3.1.

Details will be provided in the SAP.

9.3.6. Other Analyses

Actual values and percent changes from baseline in PD parameters (total IgG and [redacted]), actual values in efgartigimod serum concentrations, the presence of ADA/NAb against efgartigimod, and titers of ADA/NAb against efgartigimod will be summarized with descriptive statistics as described in Section 9.3.1.

Population PK/PD analysis may be performed based on the PK and PD data collected and reported separately. Exploratory biomarkers analyses may also be performed and reported separately.

9.4. Interim Analysis

The primary analysis will be conducted when all participants complete part A of the study. This analysis will be the final analysis for part A. Sponsor unblinding will occur at this time; however, participants and investigators will remain blinded throughout the first 2 cycles in part B.

The planned interim analysis will be described in the SAP.

After the primary analysis, additional interim analyses could be performed to support questions for authorities and/or submissions. The final analysis will occur when all participants complete the EoS or withdraw from the study.

9.5. Sample Size Determination

Approximately 110 adult participants who meet the study eligibility criteria will be stratified by MuSK-Ab status and randomized within each stratum in a 1:1 ratio to receive efgartigimod IV or placebo.

Assuming an SD of [redacted] in the efgartigimod IV arm of part A and [redacted] in the placebo arm based on ARGX-113-1704 study results in the AChR-Ab seronegative population, a total of

[redacted] participants ([redacted] in each arm) provides [redacted]% power to detect a difference in change from baseline of [redacted] in MG-ADL total score at week 4 in the efgartigimod IV arm compared to the placebo arm. The sample size calculation was performed with a 2-sample t-test with a 2-sided Type I error rate of [redacted] using Cytel East (Cytel, Cambridge, MA, United States).

Accounting for around [redacted]% attrition, approximately 110 participants will be recruited in 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 according to the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementing 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.
- A study-specific diversity plan (Section 10.7) has been prepared to ensure DEICT strategies are implemented for adequate representation of underrepresented racial and ethnic participants.
- The investigator is responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently according to the regulatory requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study 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
  - Supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient and accurate financial information as requested to allow the sponsor to submit a complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests before the study and for 1 year after study completion.

As set forth in the European regulation 536/2014 for clinical studies, principal investigators in the EEA are additionally required before study initiation to provide any interests, such as economic interests, personal interests, and institutional affiliations that can influence impartiality.

10.1.3. Informed Consent Process

- The investigator or representative will explain the nature of the study, including risks and benefits to the potential participant, and answer all questions before the participant completes the informed consent process by signing the ICF
- Potential participants must be informed that their participation is voluntary. An ICF must be signed that meets the requirements of the IRB/IEC or study center, ICH guidelines, local laws and regulations, and, where applicable, privacy and data protection requirements
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if the changes to the ICF affect participant participation
- A copy of the ICF(s) must be provided to the participant
- Participants who are rescreened are required to sign a new ICF (Section 5.4).

10.1.4. Recruitment Strategy

Patients with AChR-Ab seronegative gMG will primarily be recruited to participate in this study from the patient databases and referral networks held by the participating investigators. Where permitted by local and national regulations, patient advocacy and support groups may also be contacted to raise awareness of the study and collaborating investigators.

10.1.5. Data Protection

- The sponsor will assign participants a unique identifier. Any participant records or datasets transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that the sponsor, sponsor representatives, competent authorities, etc can review source data containing identifiers and will use their

personal study-related data per local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

- 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. IDMC

The sponsor will appoint an IDMC comprising an independent group of clinical experts (including a statistician) who are unaffiliated with this clinical study. The IDMC objective will be to review all unblinded safety data. Fixed meetings will be scheduled with timing and frequency detailed in the IDMC charter. In addition, ad hoc meetings can be requested at any time during the study by either the sponsor or the IDMC. The IDMC will advise the sponsor concerning continuation, modification, or termination of the study after every meeting.

The composition, objectives, and role and responsibilities of the IDMC will be described in the charter. The IDMC charter will also define and document the content of the safety summaries, and general procedures (including communications).

10.1.6.2. MG Diagnostic Adjudication Committee

The diagnosis of AChR-Ab seronegative gMG will be reviewed by an independent committee during the screening period. Patients for whom the diagnosis cannot be confirmed will be ineligible for this study.

A specific charter will describe the review process.

10.1.7. 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 could 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 early closure of a study site by the sponsor or investigator could include but are not limited to the following:

- For study termination:
    - Discontinuation of further compound development
- For site termination:
    - Failure of the investigator to comply with the protocol, requirements of the IRB/IEC or local health authorities, sponsor's procedures, or GCP guidelines
    - Inadequate or lack of recruitment (evaluated after a reasonable amount of time) of participants by the investigator
    - Total number of participants enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the participant and ensure appropriate therapy and/or follow-up for the participant, as necessary.

10.1.8. Dissemination of Clinical Study Data

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

10.1.9. Data Quality Assurance

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- 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.
- Guidance on completing eCRFs is provided on the eCRF completion document.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and direct access to the site and source data documents.
- Study processes, study sites (including but not limited to site visits, central laboratories, vendors), the study database, and study documentation are subject to quality assurance audit during the study by the sponsor or sponsor's designee on behalf of the sponsor. In addition, inspections could be conducted by foreign or domestic regulatory bodies at their discretion. Such audits/inspections can occur during or after study completion.
- Records and documents, including signed ICFs, on the conduct of this study must be retained by the investigator for at least 25 years after study completion unless local

regulations or institutional policies require a more extended retention period. Without the sponsor's written approval, no records will be destroyed during the retention period. No records are allowed to be transferred to another location or party without the sponsor's written approval.

- Monitoring details describing strategy and activities are outlined in a monitoring plan.
    - Study monitors will perform ongoing source data verification to confirm that data entered on the eCRF by authorized site staff 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 following the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10. Source Documents

- Source documents provide evidence of the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or else 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 investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered on the eCRF by authorized site staff 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.

10.1.11. Publication Policy

- 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 consistent with International Committee of Medical Journal Editors authorship requirements.

- A summary of results of the clinical study and a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned within 12 months as mentioned in article 37/4 of the CTR 536/2014.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 7 will be performed as described in the laboratory manual.
- Protocol-specific requirements for the inclusion and exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.
- Additional tests can be performed during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory test result.
- Refer to Section 10.8 for country-specific requirements.

Table 7: Protocol-Required Laboratory Tests

Laboratory test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH %reticulocytes	WBC count with differential: neutrophils lymphocytes monocytes eosinophils basophils
Serum chemistry	ALT AST GGT alkaline phosphatase albumin	creatinine potassium BUN CRP glucose (nonfasting)	sodium calcium bilirubin (total and direct)
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	Highly sensitive serum hCG pregnancy test at screening and urine test at other time points (as needed for WOCBP, defined in Section 10.4.1)		
Specialty laboratory tests	Eligibility serology for AChR-Ab and anti-MuSK antibodies; anti-LRP4 antibodies		
Other screening tests	• Total IgG levels • FSH to determine postmenopausal status, as necessary • HBV, HCV, HIV (refer to EC4 and Section 10.2.1.1, Section 10.2.1.2, and Section 10.2.1.3, respectively)		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; EC=exclusion criterion; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; HBV=hepatitis B virus; HCV=hepatitis C virus; IgG=immunoglobulin γ; LRP4=low-density lipoprotein receptor-related protein 4; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell; WOCBP=women of childbearing potential

10.2.1. Other Screening Tests

10.2.1.1. Hepatitis B Virus

Active acute or chronic HBV is exclusionary. Participants with an active acute or chronic HBV at screening will be excluded from the study.

The serologic marker combinations shown in Table 8 will be used to identify an active HBV infection.

Table 8: Interpretation of Hepatitis B Serological Test Results

Test result			
HBsAg	**Anti-HBc**	**Anti-HBs**	**Interpretation**
Positive	Positive	Negative	An active HBV infection is exclusionary
Negative	Positive	Negative	Occult infection or mutant HBsAg strain infection undetectable by laboratory assay is exclusionary

anti-HBc=total hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus
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

An active acute or chronic HCV infection is exclusionary. The HCV antibody serologic test will identify an active infection as indicated in Table 9.

Table 9: 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

Ab=antibody; HCV=hepatitis C virus

10.2.1.3. Human Immunodeficiency Virus

Participants who are HIV positive may be included in the study if all of the following conditions are met:

- CD4 count is ≥200 cells/mm^3 (Table 10)
- Viral load is <200 copies/mL or undetectable (Table 10)
- Participant has been receiving stable antiretroviral therapy for at least 3 months (minimally) before screening
- AIDS-defining condition is absent

AIDS-defining conditions include the following:

- Cytomegalovirus retinitis with loss of vision
- *Pneumocystis jiroveci* pneumonia

- Chronic intestinal cryptosporidiosis
- Mycobacterium tuberculosis (pulmonary or extrapulmonary)
- HIV-related encephalopathy
- Invasive cervical cancer

Table 10: Interpretation of HIV Test Results

HIV test result	Clinical condition/ CD4 count/viral load	Interpretation
Positive	AIDS-defining condition present or CD4 <200 cells/mm^3	Test results and clinical conditions or CD4 count confirm AIDS diagnosis, which is exclusionary
	Viral load >200 copies/mL despite participant receiving antiretroviral therapy	Participant ineligible because the antiretroviral therapy is not adequate
	Viral load <200 copies/mL but participant not receiving antiretroviral therapy	Participant ineligible because not receiving antiretroviral therapy

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 AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. • 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 IMP.
Events to Be Collected as AEs
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign 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 IMP administration even though it could 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 IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses will 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:

Results in death

Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted 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 is considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from screening will not be collected as an AE.

Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include events of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that can interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment will be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that could jeopardize the participant or require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are usually 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 considered 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 required form.
- There can 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.
- The sponsor shall keep detailed records of all AE reported by the investigator.
- If the investigator becomes aware of a SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

Assessment of Severity

The investigator will assess intensity for each AE and SAE reported during the study.

All AEs observed will be graded using the NCI-CTCAE definitions current version.

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 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 may not necessarily meet the criteria for an SAE. Severe is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe. Grade 4 and 5 AEs are always assessed as serious (ie, SAE).

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 IMP administration, will be considered and investigated.

- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP administration is compelling and/or follows a known or suspected response pattern concerning that IMP.
- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP and the AE.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.

There could be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.

- The investigator could change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This could 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 updated SAE data within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs and AESIs

SAE and AESI Reporting

- All SAEs and AESIs will be recorded on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form.
- The investigator or designated site staff will ensure all entered data are consistent.
- An alert email for the SAE and AESI reports on the eCRF will automatically be sent by email to the sponsor or designee's safety mailbox via the EDC system.
- The paper SAE report form will be faxed or emailed to the sponsor's designee (refer to the Serious Adverse Event Reporting details on page 1 of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Women of Childbearing Potential Definition

A female is considered a WOCBP unless she is either:

- Postmenopausal: FSH measurement compatible with menopause. If the participant is receiving hormone replacement therapy: continuous amenorrhea for at least 1 year and investigator assessment that the participant is postmenopausal
- 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

The following Clinical Trials Facilitation and Coordination Group[47] methods are permitted for efgartigimod studies:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Combined (estrogen-containing and progestogen-containing) hormonal contraception associated with ovulation inhibition:
  - Oral
  - Intravaginal
  - Transdermal
- 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
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

10.4.2.2. Male Contraception

No male contraception is required.

10.5. Appendix 5: Operational Considerations for COVID-19 Risk Mitigation

This appendix is intended for use only if unforeseen changes in the COVID-19 pandemic result in new restrictions at the site or new risks for participants or site staff from attending visits at the site.

Additional testing for COVID-19 is not required during the study unless required by local authorities. However, it is recommended that participants who develop COVID-19 symptoms while receiving IMP be tested, with results reported for the study.

Critical Parameters to Be Collected During the Study

All assessments will be performed as indicated in the SoA (Section 1.3). If assessments cannot be performed because of the COVID-19 pandemic, the following information must be collected from the first visit through the end of study:

- all AE and concomitant medication reporting
- infusion/injection-related reactions
- IMP administration
- questionnaires
- QMG assessments

10.6. Appendix 6: Home Study Visits

Not applicable.

10.7. Appendix 7: Race and Ethnicity Diversity Plan

Refer to the guidance on diversity.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. China

All biological samples collected in participants in China will be analyzed according to local laws and regulations.

Biological samples collected at screening from participants in China can be used to validate methods to measure antibodies, biomarkers, and efgartigimod. Such use of these samples is only permitted after obtaining approval from the Human Genetic Resources authority, and the methods in which they are used must comply with local regulations. The conditions under which these samples are stored and ultimately destroyed will comply with Human Genetic Resources authority requirements and other relevant regulations.

10.9. Appendix 9: Protocol Amendment History

Summary of Changes Table: Amendment 1 (03 Sep 2024)

Section	**Change in study conduct or planned analysis**	**Brief rationale**
1.1 Synopsis	Addition of EU-CT number, secondary endpoints, and Ethics considerations. Adaptation to maintain 2 pages in length.	Adaptation to EU-CTR requirements.
4.1 Overall Design Other sections impacted 10.1.6.1 IDMC	~~To evaluate the benefit-risk balance, an interim analysis for futility (nonbinding) will be conducted (Section 10.1.6.1). The IDMC will discuss the collected efficacy results and provide recommendations to the sponsor to terminate or continue the study.~~	Futility analysis will not be conducted in this study and therefore information has been removed.
5.1 Inclusion Criteria Inclusion Criterion 1	1. Is at least **18 years of age and** the local legal age of consent for clinical studies when signing the ICF	To clarify the consent age.
5.2 Exclusion Criteria	**18. The participant has any relationship of dependency with the sponsor.**	To exclude participants who could have a conflict of interest with the sponsor

Section	Change in study conduct or planned analysis	Brief rationale
8.4.4 Regulatory Reporting Requirements for SAEs	The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities **via the appropriate reporting systems (eg, Eudravigilance and FDA AE reporting system),** ~~and IEC/IRB~~ per applicable regulatory requirements.	To clarify SUSAR reporting in the study
9.1.1 Multiplicity Adjustment	**Given the cumulative efficacy data of efgartigimod in AChR-Ab seronegative patients with gMG and the fact that the study includes a rare subset of an already rare disease**, a closed testing procedure that controls the family-wise error rate in the strong sense at the overall [redacted]% level will be applied.	To clarify the use of a relaxed type I error rate in the study.
9.2 Analysis Sets	Safety analysis set (part A): All participants who received at least 1 IMP dose **or part of a dose** in part A Safety analysis set (part A+B): All participants who received at least 1 dose of efgartigimod IV **or part of a dose** in part A or B	Safety analysis sets were changed to include participants who received part of a dose.
9.5 Sample Size Determination	Accounting for **around** [redacted]% attrition, ~~a total of~~ **approximately** 110 participants will be recruited in the study.	To clarify the sample size determination when accounting for attrition.
9.5 Sample Size Determination	~~Assuming [redacted]% and [redacted]% of participants in the efgartigimod IV arm and placebo arm, respectively, are responders on both the MG-ADL and QMG scales, a sample size of [redacted] will provide [redacted]% power to detect the difference of [redacted]% in response rates between the 2 arms with a 2-sided α level of [redacted]~~	To clearly indicate that the sample size determination is based on the primary endpoint only.
10.1.1 Regulatory and Ethical Considerations	o Providing written summaries of the status of the study to the IRB/IEC annually or more frequently according to the **regulatory** requirements, policies, and procedures established by the IRB/IEC [...]	To clarify investigator responsibilities.

Section	Change in study conduct or planned analysis	Brief rationale
	o **Supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.**	
10.1.6.1 IDMC	~~To evaluate the benefit-risk balance, an interim analysis for futility (nonbinding) will be conducted. The IDMC will discuss obtained efficacy results, and provide recommendations to the sponsor to terminate or continue the study. Timing, frequency, and futility rules will also be described in the IDMC charter.~~	Futility analysis will not be conducted in this study and therefore information has been removed.
10.1.11 Publication Policy	**A summary of results of the clinical study and a summary that is understandable to a layperson will be provided after the global end (or early termination) of the study in all countries concerned within 12 months as mentioned in article 37/4 of the CTR 536/2014.**	To clarify reporting of the study data based on article 37/4 of the CTR 536/2014. Not previously included in the protocol.
10.2 Appendix 2: Clinical Laboratory Test	Table 7 ~~SARS-CoV-2 nasopharyngeal swab test~~	Removal of protocol specific assessment for COVID-19.
10.2.1.1 SARS-CoV-2	~~10.2.1.1 SARS-CoV-2~~ ~~Participants will be tested for SARS-CoV-2 if they are symptomatic or if local laws require testing. If local laws require testing, the participant must have a negative PCR test (central or local laboratory) result within 72 hours before enrollment regardless of a participant's vaccination status. A positive test at screening is not exclusionary. The participant may be included in the study after a subsequent negative test and clinical recovery without rescreening if recovery occurs within the 5-week screening period~~	Removal of protocol specific assessment for COVID-19.

Section	Change in study conduct or planned analysis	Brief rationale
10.3.3 Recording and Follow-up of AE and/or SAE	• **The sponsor shall keep detailed records of all AE reported by the investigator.** • **If the investigator becomes aware of a SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.**	To clarify Sponsor and Investigator responsibilities.
10.5 Appendix 5: Operational Considerations for COVID-19 Risk Mitigation	~~Participants will be tested for SARS-CoV-2 if they are symptomatic or if local laws require testing. If local laws require testing, the participant must have a negative PCR test (central or local laboratory) result within 72 hours before enrollment regardless of a participant's vaccination status.~~ ~~During the study, the sites will implement all recommendations issued by the local government regarding COVID-19, including specific guidelines related to clinical research performed in clinical research centers. This appendix is intended for use only if unforeseen changes in the COVID-19 pandemic result in new restrictions at the site or new risks for participants or site staff from attending visits at the site.~~ […] Additional testing for COVID-19 ~~beyond what is listed in the SoA (Section 1.3)~~ is not required during the study unless required by local authorities. However, it is recommended that participants who develop COVID-19 symptoms while receiving IMP be tested, with results reported for the study.	Removal of protocol specific assessment for COVID-19.

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