TITLE PAGE

Protocol Title:	A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness
Protocol Number:	ARGX-113-1705 (ADAPT+)
Date of Protocol:	19 Jan 2021, Version 4.0, Final
Product:	Efgartigimod (ARGX-113)
IND No:	[redacted]
EudraCT No:	2018-002133-37
Trial Phase:	3
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The following additional numbers are also available for urgent contact

24-Hour Urgent Medical Helpline Number:	+1 877 462 0134

For drug-safety reporting, contact the below email address

Safety Mailbox/Fax:	Email: 248700ADR@parexel.com Fax: +1 833 644 0806

Confidentiality Statement

This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the sponsor.

SIGNATURE OF SPONSOR

PROTOCOL TITLE: A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness

PROTOCOL NO: ARGX-113-1705 (ADAPT+)

SPONSOR REPRESENTATIVE:

[redacted]

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[redacted], MD **Sig** **Date**
Chief Medical Officer
argenx BVBA

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness

PROTOCOL NO: ARGX-113-1705 (ADAPT+)

This protocol is a confidential communication of argenx BVBA. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx BVBA.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the trial will be conducted. Return the signed original copy to the local representative of your sponsor's designated CRO.

I have read this protocol in its entirety and agree to conduct the trial accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

DOCUMENT HISTORY

Previous Version Number	Effective Date
Protocol Version 1.0	15 June 2018
Protocol Version 2.0	12 August 2019
Protocol Version 3.0	18 December 2019
Protocol Version 3.1	15 April 2020
Protocol Version 3.2	30 June 2020
Protocol Version 4.0	19 January 2021

SUMMARY OF CHANGES

Changes from Protocol Version 3.2 compared to Protocol Version 4.0 are summarized below.

Note: updates to headers/footers and the tables of contents and editorial changes to layout, font, format, and style guide conventions are not captured in this summary.

Section	Change	Rationale
Safety Mailbox/Fax:	Email: be.life.saefax-ma@sgs.com Fax: +32 (0)15 29 93 94 changed to Email: 248700ADR@parexel.com Fax: +1 1 833 644-0806	Parexel is replacing SGS as the CRO for safety reporting.
Appendix 4 Administrative Structure	Added vendor for study monitoring EastHORN Clinical Service GmbH Im Mediapark 6c 50670 Cologne Germany	Corrected an omission of a monitoring vendor
	Data Management, Biostatistics, Drug Safety Reporting changed to Data Management and Biostatistics	SGS is the CRO for data management and biostatistics. Parexel is the CRO for drug safety reporting.
	Row added for safety reporting vendor Drug Safety Reporting Parexel International 8 Federal Street	

Section	Change	Rationale
	Billerica MA 01821 United States	
Throughout document	ARGX-113 changed to efgartigimod	ARGX-113 has been changed to efgartigimod throughout the document to be current with the clinical development program.
1.4. Benefit-Risk Assessment	The section has been revised.	Updated benefit-risk assessment based on emerging data and consistency with IB v9.0
4.1. Summary of Trial Design Other sections impacted by the added text: • Synopsis • Table 2 General Schedule of Assessments for Part B • Figure 2 ARGX-113-1705 Trial Design for Part B • Section 1.4 Benefit-Risk Assessment • 4.2. Discussion of Trial Design	Added text: Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration. Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002. Patients can enroll in ARGX-113-2002 until recruitment for this study is closed. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.	To allow patients to enroll in the safety study ARGX-113-2002
4.4. Early Discontinuation Other sections impacted by the changed text: • 5.4 End of Part A, End of Study and Early Discontinuation Visit	…contact those patients who do not return for scheduled visits. The reason for early discontinuation from the trial will be clearly documented by the Investigator. Changed to …contact those patients who do not return for scheduled visits. Patients enrolling in ARGX-113-2002 from Part B must first complete the ED visit assessments from ARGX-113-1705 (see Table 2). Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.	To provide end of trial instruction for patients who enroll in study ARGX-113-2002

Section	Change	Rationale
	The reason for premature discontinuation from the trial must be documented by the investigator on the appropriate page of the eCRF.	
5.2.1. Treatment Period Part A Other sections impacted by the changed text: • Synopsis • Table 1 General Schedule of Assessments for Part A (footnote c) • 4.1. Summary of Trial Design	If a patient becomes eligible for (re-)treatment with efgartigimod per total MG-ADL score but cannot complete the entire treatment period within the duration of Part A of the trial (re-treatment in Part A can start at the latest by day 336) the patient can be transitioned to Part B after completing the end of Part A (EoA) visit. If the patient is not willing or able to continue to Part B then he/she should continue to the EoA visit. changed to If a patient becomes eligible for (re-)treatment with efgartigimod by meeting the criteria for the total MG-ADL score as stated in Section 4.1, but cannot complete the entire treatment period within Part A (ie, after day 336) then the patient can be transitioned to Part B after completing the EoA visit assessments (Table 1). These assessments should be completed even if the patient is unwilling or unable to continue to Part B (see Section 5.1).	Revised for clarity
4.3.2. Exclusion Criteria Other sections impacted by the moved text: • Synopsis	Instruction on contraception requirements moved to Appendix 9.	Contraceptive requirements were removed from the Exclusion Criterion section for logical reasons.
Appendix 9: Contraceptive and Barrier Guidance	Updated contraception requirements to allow for “acceptable” contraception methods per CTFG guidelines.	Guidance on contraception has been updated following results of nonclinical reproductive toxicity studies.
6. TRIAL TREATMENT 6.8. Prior Treatments and Concomitant Medications Other sections impacted by the added text: • Table 1 General Schedule of Assessments for Part A (footnote s)	Added text: Any vaccination received within 28 days of screening up until 28 days after the final dose of the IMP should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration.	Instructions were added to collect vaccination history.

Section	Change	Rationale
• Figure 1: ARGX-113-1705 Trial Design for Part A • Table 2 General Schedule of Assessments for Part B (footnote q) • Figure 2: ARGX-113-1705 Trial Design for Part B		
7.2.3. Vital Signs, Physical Examination, and ECG Other sections impacted by the added assessment: • Table 2 General Schedule of Assessments for Part B (footnote k) • 5.2.2. Trial Period Part B and 5.3. Inter Treatment Period • 5.4. End of Part A, End of Study and Early Discontinuation Visit • 7.2 Safety	ECG assessment added to Part B	The ECG assessment was added to Part B to comply with the DSMB recommendation to monitor QTcF abnormalities that could arise due to the accumulation of efgartigimod.
9.3 Monitoring	Added text: Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.	Clarification

An additional change was made to allow for testing in patients exhibiting symptoms of COVID-19 infection.

Even in countries where COVID-19 safety measures are stopped according to local regulations, COVID-19 testing should continue and the results sent to the sponsor for filing.

Section	Change	Rationale
Table 1 General Schedule of Assessments for Part A and Table 2 General Schedule of Assessments for Part B	Bold italics added to Table 1 and Table 2.	The assessments identified for telephone assessment visits are highlighted in bold italics in the existing Schedule of Assessments for Part A in Table 1 and for Part B in Table 2.
	Footnote added: Assessments highlighted by the use of bold italics indicate assessments that may be carried out as a telephone assessment visit under the conditions outlined in Appendix 8.	
Appendices	Appendix 8 added.	An addendum has been added to the study detailing the safety measures and changes to be implemented in the current situation.

Due to the number of changes, and therefore the size of the tables required to describe all the changes made to the protocol, the detailed Summary of Changes tables have been moved to Appendix 7.

For the global amendment of the ARGX-113-1705 protocol from version 2.0 to 3.0 an additional part (Part B) has been added to the trial in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension to Part A of the trial will be a maximum of 2 years and will also enable additional long-term safety and tolerability data to be collected. Below is a comparison of the differences between Part A and Part B of the trial:

Subject	Part A (1 year)	Part B (max 2 years)
Intertreatment period visits	30 days after the previous visit	90 days after the previous visit
Disease severity assessments	MG-ADL and QMG	MG-ADL only
Other assessments	As per Table 1.	As per Table 2: Fewer assessments to reduce burden for the patient: No suicidality assessments, ECG, anti-AChR/anti-MuSK antibodies and total IgG and its subtypes
Laboratory testing	Central laboratory for clinical laboratory tests (hematology, clinical chemistry)	Local laboratory for clinical laboratory tests (hematology, clinical chemistry)

Subject	**Part A (1 year)**	**Part B (max 2 years)**
Standard of care (SoC)	From 1 week after the last infusion of each Treatment Period up to and prior to the administration of the first infusion of the next Treatment Period, a dose reduction in SoC consistent with current medical practice is allowed	Change of SoC allowed
Rescue therapy	Rescue therapy limited	Not applicable
Prohibited medications	List of prohibited medications	No prohibited medications
Safety and disease severity follow-up period	Has been removed from the current protocol amendment	Not applicable

AChR=acetylcholine receptor; ECG=electrocardiogram; IgG=immunoglobulin gamma; MG-ADL=Myasthenia Gravis Activities of Daily Living; MuSK=Muscle-Specific Kinase; QMG=Quantitative Myasthenia Gravis score; SoC=Standard of Care

SYNOPSIS

Name of Sponsor:	**argenx**
Name of Investigational Medicinal Product (IMP):	**Efgartigimod (ARGX-113)**
Name of Active Ingredient:	A human anti-neonatal crystallizable fragment (Fc) receptor (FcRn) immunoglobulin G1 (IgG1) Fc fragment
Indication:	Treatment of patients with generalized myasthenia gravis (gMG)
Title of Trial:	A Long-Term, Single-Arm, Open-Label, Multicenter, Phase 3 Follow-on Trial of ARGX-113-1704 to Evaluate the Safety and Tolerability of ARGX-113 in Patients With Myasthenia Gravis Having Generalized Muscle Weakness
Protocol No:	ARGX-113-1705 (ADAPT+)
Trial Sites:	This trial is an extension of trial ARGX-113-1704 and will be conducted in the sites that participated in the ARGX-113-1704 trial

Trial Duration: The trial duration will be up to maximum 3 years. The trial consists of 2 parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration.	**Phase:** 3

Objectives:

Primary Objective:

- To evaluate the long-term safety and tolerability of efgartigimod in acetylcholine receptor antibody (AChR-Ab) seropositive patients

Secondary Objective:

- To evaluate the long-term safety and tolerability of efgartigimod in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients)

Tertiary Objectives:

Part A only:

- To evaluate the disease severity as assessed by total Myasthenia Gravis Activities of Daily Living (MG-ADL) score changes in AChR-Ab seropositive patients.
- To evaluate the disease severity as assessed by total MG-ADL score changes in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).
- To evaluate disease severity as assessed by total Quantitative Myasthenia Gravis (QMG) score changes in AChR-Ab seropositive patients.
- To evaluate disease severity as assessed by total QMG score changes in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).

- To evaluate the effect of efgartigimod on pharmacodynamics (PD) (total immunoglobulin gamma [IgG], IgG subtypes, autoantibodies [anti-AChR antibodies and anti-muscle-specific kinase (MuSK) antibodies]).

Part A and B:

- To evaluate the immunogenicity of efgartigimod.

Methodology:

DESCRIPTION

This is a 3-year (maximum), single-arm, open-label, multicenter, phase 3 follow-on trial of ARGX-113-1704 to evaluate the long-term safety and tolerability of efgartigimod in patients with gMG. The trial consists of 2 parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). The additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension will also enable additional long-term safety and tolerability data to be collected.

A variable number of treatment periods consisting of 4 weekly infusions of efgartigimod (10 mg/kg of body weight) infused over a period of 3 weeks will be administered to eligible patients on an "as needed basis" on top of their standard of care (SoC). The time between treatment periods is based on the duration of the treatment effect and may vary from patient to patient and within each patient from period to period (patient-tailored approach).

The first visit of trial ARGX-113-1705 will coincide with the last visit of trial ARGX-113-1704 for each patient.

The study entry baseline (SEB) will be set at the first trial visit, while the baseline of each subsequent treatment period (TP_nB for Part A or TPE_nB for Part B) will be set at visit 1 of each corresponding treatment period.

ROLL-OVER

At the end of study (EoS) visit of trial ARGX-113-1704, eligible patients will be offered the option to roll over into this trial. Patients in need of (re-)treatment in trial ARGX-113-1704 but who cannot complete a Treatment Cycle within the time frame of that trial, may immediately roll over to this trial to receive treatment with efgartigimod.

Patients who discontinued early from trial ARGX-113-1704 or discontinued early from randomized treatment for rescue or pregnancy reasons or for a serious adverse event (SAE) that is likely to result in a life-threatening situation or pose a serious safety risk in that trial will not be offered the option to roll over into this trial.

Patients who discontinued early from randomized treatment for other reasons and patients who had a temporary interruption from randomized treatment in trial ARGX-113-1704 may be offered the option to roll over into this trial.

Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration.

Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002.

Patients can enroll in ARGX-113-2002 until its recruitment has closed. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.

(RE-)TREATMENT (Part A)

Each patient will start a (new) treatment period with efgartigimod when all the following criteria apply:

- The patient has completed the previous treatment period (ie, after visit 4)
- The patient has a total MG-ADL score of ≥5 points with more than 50% of the total score due to non-ocular symptoms
- The patient has a reduction in the MG-ADL total score of <2 points compared to the score at:
  1. The last treatment cycle baseline (TCB) in trial ARGX-113-1704 for the first treatment period (TP_1) in trial ARGX-113-1705
  2. The last treatment period baseline (TP_nB) for all subsequent treatment periods (TP_{n+1}) in trial ARGX-113-1705

However, patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. Patients who are in need of an additional treatment but who are not eligible to receive (re-)treatment for reasons listed here will remain in the trial to receive appropriate alternative MG treatment (see Appendix 5 and Appendix 6).

Patients who show a treatment failure to efgartigimod for 3 consecutive treatment periods will be discontinued from the trial. Treatment failure means the absence of a decrease of at least 2 points in total MG-ADL score compared to the corresponding TP_nB in at least 50% of the assessments (ie, TP_nV2, TP_nV3, TP_nV4 and the first posttreatment period visit).

If a patient becomes eligible for (re-)treatment with efgartigimod by meeting the criteria for the total MG-ADL score as stated in Section 4.1, but cannot complete the entire treatment period during Part A (ie, after day 336) then the patient can be transitioned to Part B after completing the end of Part A (EoA) visit assessments (Table 1). These assessments should be completed even if the patient is unwilling or unable to continue to Part B (see Section 5.1).

The transition to Part B can be either at $ITPE_0V1$ or TPE_1V1, depending on the patient's status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.

(RE-)TREATMENT (Part B)

If the patient feels that his/her condition has deteriorated, then the investigator may start a new treatment period at an intertreatment period (ITPE) visit or the patient may contact the investigator to attend an unscheduled visit.

A patient can start the next treatment period and receive efgartigimod if all of the following criteria are met:

- The patient has completed the previous treatment period (ie, after visit 4)*
- The investigator determines that the patient will benefit from re-treatment
- There is at least 1 calendar month (minimum 4 weeks) between treatment periods (ie, between TPE_nV4 and $TPE_{n+1}V1$)

*A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions in Section 4.4.1 are met.

However, patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk.

If a patient becomes eligible for (re-)treatment with efgartigimod but cannot complete the entire treatment period within the duration of the trial, the patient should continue to the EoS visit.

If the investigator considers that the patient will not have a clinical benefit from (re-)treatment then the patient cannot start a new treatment period. The patient should then continue to the EoS visit.

STANDARD OF CARE (SoC)

In Part A:

Permitted SoC for MG treatment under this protocol include NSIDs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as acetylcholinesterase (AChE) inhibitors.

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed:

- From trial entry until 1 week after the last infusion of the first treatment period.
- From the first infusion until 1 week after the last infusion of each subsequent treatment period.

From 1 week after the last infusion of each treatment period up to and prior to the administration of the first infusion of the next treatment period, a dose reduction in SoC consistent with current medical practice is allowed.

In case these medications are taken for another indication than MG, same conditions apply.

Administration of AChE inhibitors must be halted for at least 12 hours prior to performing the QMG assessment. Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC.

In Part B:

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice.

Plasma exchange (PLEX), intravenous immunoglobulin (IVIg), immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.

TIME BETWEEN TREATMENT PERIODS

At the end of each treatment period, patients will enter a variable intertreatment period during which they will be treated with their SoC only. The length of the intertreatment period may vary from patient to patient and for each patient from period to period (patient-tailored approach). For Part A, the visit frequency in the intertreatment period is every 30 days (± 2 days) after the previous visit. For Part B, the visit frequency in the intertreatment period is every 90 days (± 7 days) after the previous visit. If an inter-treatment period (ITP) visit for Part A is scheduled within 14 days of the EoA visit, then the EoA visit should be performed instead.

RESCUE THERAPY (Part A only)

Rescue therapy will be limited to PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination.

Rescue therapy is permitted for patients experiencing protocol-defined MG clinical deterioration AND if in addition the treating physician believes that the patient's health is in jeopardy if rescue therapy is not given. An MG clinical deterioration permitting rescue therapy to be given is defined as a patient experiencing at least 1 of the following: (1) new or worsening of respiratory / bulbar symptoms or (2) at least 2-point increase of individual non-ocular MG-ADL items. Whenever possible, prior to giving rescue therapy to a patient, the Medical Director at the sponsor and the Medical Monitor at the sponsor's designated Contract Research Organization (CRO) should be informed.

In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from the trial.

EARLY DISCONTINUATION

For patients who discontinue early from the trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4, Figure 1, and Figure 2).

Patients who discontinue early from the trial within a treatment period should perform the planned assessments of the corresponding treatment period visit. These patients will not receive any further administration of efgartigimod during the trial and will return for the ED visit 1 month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the investigator.

Patients who discontinue early from the trial between the last visit of a treatment period (TP_nV4 or TPE_nV4) and the next intertreatment period visit (ITP_nVn or $ITPE_nVn$) should perform the ED assessments 1 month (30 ± 2 days) after the last dose administration.

Patients who discontinue early from the trial at the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments, instead of the ITP_nVn (Part A) or $ITPE_nVn$ (Part B) assessments.

Patients who discontinue early from the trial after the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments.

Any patient prematurely discontinuing the trial during Part A should perform the EoA/ED assessments according to the General Schedule of Assessments for Part A (Table 1). Any patient prematurely discontinuing the trial during Part B should perform the EoS/ED assessments according to the General Schedule of Assessments for Part B (Table 2).

Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.

TEMPORARY INTERRUPTION FROM TRIAL TREATMENT

A patient who does not need to be discontinued early from the trial might still have a temporary interruption from trial treatment which is defined as a discontinuation only from the current treatment period. Therefore, these patients might still be eligible for further additional treatments with efgartigimod within this trial.

Patients for whom treatment is interrupted will have to complete the current treatment period and will continue the trial as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2) but without drug administration. A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions mentioned above are met.

Planned Number of Patients:	The maximum number of patients in this trial will be the number of patients who participated in trial ARGX-113-1704.

Criteria for Inclusion and Exclusion:	**Inclusion Criteria:** 1. Patients with the ability to understand the requirements of the trial, provide written informed consent, and can comply with the trial protocol procedures. 2. Patients who participated in trial ARGX-113-1704 and are eligible for roll over, ie: • Patients who reached EoS at day 182 in trial ARGX-113-1704. • Patients who need (re-)treatment in trial ARGX-113-1704 but cannot complete a Treatment Cycle within the time frame of that trial may immediately roll over into this trial to receive treatment with efgartigimod. • Patients who discontinued early from randomized treatment for other reasons than pregnancy, rescue therapy or an (S)AE in trial ARGX-113-1704 may be offered the option to roll over into this trial. • Patients who had a temporary interruption from randomized treatment in trial ARGX-113-1704 may be offered the option to roll over into this trial. 3. Patients are required to be on a stable dose of their MG treatment (SoC) prior to SEB. The SoC is limited to acetylcholinesterase (AChE) inhibitors, steroids and non-steroidal immunosuppressive drugs (NSIDs) (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide). Note: AChE inhibitors must be withheld for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America (MGFA), before the QMG assessment.
	Exclusion Criteria: 1. Patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from randomized treatment for rescue or pregnancy reasons or an SAE that is likely to result in a life-threatening situation or pose a serious safety risk. 2. Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing. Women of childbearing potential (DEFINITION OF TERMS) should have a negative urine pregnancy test at SEB. The contraceptive requirements for women of childbearing potential are described in **Error! Not a valid result for table.**. 3. Male patients who are sexually active and do not intend to use effective methods of contraception (as mentioned above) during the trial or within 90 days after the last

	dosing or male patients who plan to donate sperm during the trial or within 90 days after the last dosing. The contraceptive requirements for male patients are described in **Error! Not a valid result for table.**. 4. Patients with known hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) seropositivity. 5. Patients with known autoimmune disease other than MG (for example autoimmune thyroiditis, rheumatoid arthritis, …) that would interfere with an accurate assessment of clinical symptoms. 6. Patients with clinical evidence of other significant disease or patients who underwent a recent major surgery, which could confound the results of the trial or put the patient at undue risk. Patients with renal/hepatic function impairment can be included. 7. Patients with known medical history of hypersensitivity to any of the ingredients of efgartigimod.
Test Product, Dose, and Mode of Administration:	In this trial, the test product is efgartigimod (ARGX-113), which is a human anti-FcRn IgG1 Fc fragment. In patients who need (re)-treatment, a dose of 10 mg/kg of body weight of efgartigimod will be administered at visits 1, 2, 3, and 4 of each treatment period as an intravenous (IV) infusion over a period of 1 hour. The total dose per efgartigimod infusion is capped at 1200 mg for patients with body weight ≥120 kg.

Criteria for Evaluation:

Primary Endpoint:

- Incidence and severity of AEs, SAEs, vital signs, electrocardiogram (ECG) and laboratory assessments over the duration of the trial in AChR-Ab seropositive patients.

Secondary Endpoint:

- Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments over the duration of the trial in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).

Tertiary Endpoints:

Part A only:

- Total MG-ADL score changes compared to the treatment period baseline of the first cycle (TP_1B) and the corresponding TP_nB in AChR-Ab seropositive patients.
- Total MG-ADL score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Total QMG score changes compared to TP_1B and the corresponding TP_nB in AChR-Ab seropositive patients.
- Total QMG score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

- Percentage decrease (compared to TP_1B and the corresponding TP_nB) of total IgG level and IgG subtypes in efgartigimod (re-)treated patients.
- Percentage decrease (compared to TP_1B and the corresponding TP_nB) of autoantibodies (anti-AChR antibodies and anti-MuSK antibodies) in efgartigimod (re-)treated patients.

Part A and B:

- Incidence and prevalence of anti-drug antibodies (ADA) to efgartigimod.

Statistical Methods and Plan:

A Statistical Analysis Plan detailing all statistical methods and analyses will be issued before any database lock. A summary of the plan is described below.

All endpoints will be summarized in all enrolled patients by means of descriptive statistics.

Summary statistics will be provided for the continuous endpoints (eg, total MG-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies, laboratory values, vital signs, ECG) in terms of absolute values, changes from TP_1B or changes from TP_nB, by cycle and available time points.

Frequency tables will be made for all binary variables, ie, AEs and ADA by cycle and overall.

Table 1 General Schedule of Assessments for Part A

Assessment	Roll-Over Visit[a]	Treatment Period				Intertreatment Period[a,b,c]	End of Part A[c]/ Early Discontinuation[d]	Unscheduled[e]
Visits Treatment Period 1	**SEB**	**TP_1V1[a]**	**TP_1V2**	**TP_1V3**	**TP_1V4**	**ITP_nVn**	**EoA/ED**	**UNS**
Trial Day (Visit Window)		**1**	**8±1**	**15±1**	**22±1**			
Visits Subsequent Treatment Periods		**TP_nV1 (TP_nB)**	**TP_nV2**	**TP_nV3**	**TP_nV4**			
Trial Day (Visit Windows)		**X**	**(X+7)±1**	**(X+14)±1**	**(X+21)±1**	**Y + 30 (±2)**	**365±7**	
***Informed consent*[f]	*X*							
In- and exclusion criteria	X							
Medical/surgical history	X							
Demographic characteristics	X							
***MG-ADL*[g]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
QMG[g]	X	X	X	X	X	X	X	X
Suicidality assessment[h]	X	X	X	X	X	X	X	X
Physical examination[i]	X	X	X	X	X	X	X	X
Weight and height[j]	X						X	
Vital signs[k]	X	X	X	X	X	X	X	X
ECG[l]	X	X			X	X	X	X
Clinical laboratory tests[m]	X	X	X	X	X	X	X	X
Urinalysis[n]	X	X	X	X	X	X	X	X
Urine pregnancy test[o]	X	X	X	X	X	X	X	X
Anti-AChR/anti-MuSK antibodies[p]	X	X	X	X	X	X	X	X
Total IgG and its subtypes[p]	X	X	X	X	X	X	X	X

Assessment	Roll-Over Visit[a]	Treatment Period				Intertreatment Period[a,b,c]	End of Part A[c]/ Early Discontinuation[d]	Unscheduled[e]
Visits Treatment Period 1	**SEB**	**TP_1V1[a]**	**TP_1V2**	**TP_1V3**	**TP_1V4**	**ITP_nVn**	**EoA/ED**	**UNS**
Trial Day (Visit Window)		**1**	**8±1**	**15±1**	**22±1**			
Visits Subsequent Treatment Periods		**TP_nV1 (TP_nB)**	**TP_nV2**	**TP_nV3**	**TP_nV4**			
Trial Day (Visit Windows)		**X**	**(X+7)±1**	**(X+14)±1**	**(X+21)±1**	**Y + 30 (±2)**	**365±7**	
ADA[q]	X	X			X		X	
Efgartigimod administration[r]		X	X	X	X			
***Prior/concomitant/rescue therapy**[s]	<----------X---------->							
***Adverse events**	<----------X---------->							

AChR=acetylcholine receptor; ADA=anti-drug antibodies; ECG=electrocardiogram; EoA/ED=end of Part A/early discontinuation; EoS=end of study; QMG=Quantitative Myasthenia Gravis score; IgG=immunoglobulin gamma; ITPV=intertreatment period visit; MG-ADL=Myasthenia Gravis Activities of Daily Living; MuSK=muscle-specific kinase; SEB=study entry baseline; TPB=treatment period baseline; TPV=treatment period visit; Y=previous visit; UNS=unscheduled visit

[a] The roll-over visit can be either at ITP0V1 or TP1V1, depending on the patient status regarding the need for (re-)treatment upon roll-over from trial ARGX-113-1704. The first visit in trial ARGX-113-1705 will always coincide with the EoS visit in trial ARGX-113-1704. The assessments done for the last visit in trial ARGX-113-1704 should not be repeated.

[b] The intertreatment period visits (ITPnVn) occur every 30 days after the previous visit (Y). The visit denominator ("n") will start at 1 at each period. At each ITPnVn, an evaluation of the need for (re-)treatment should be done prior to deciding whether the assessments listed for ITPnVn or TPnV1 are to be performed. If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then this EoA visit should be performed instead. For patients that discontinue at the ITP visit this will then serve as the EoA/ED visit.

[c] If a patient becomes eligible for (re-)treatment with efgartigimod by meeting the criteria for the total MG-ADL score as stated in Section 4.1, but cannot complete the entire treatment period during Part A (ie, after day 336), then the patient can be transitioned to Part B after completing the EoA visit assessments. These assessments should be completed even if the patient is unwilling or unable to continue to Part B (see Section 5.1). The transition to Part B can be either at ITPE0Vn or TPE1V1, depending on the patient status regarding the need for (re)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.

[d] For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4). Patients who discontinue early from the trial within a treatment period should perform the planned assessments of the corresponding treatment period visit. These patients will not receive any further administration of efgartigimod during the trial and will return for the ED visit 1 month (30 ± 2 days)

after the last dose administration. An unscheduled visit can be organized if deemed necessary by the investigator. Patients who discontinue early from the trial between the last visit of a treatment period (TPnV4) and the next intertreatment period visit (ITPnVn) should perform the ED assessments 1 month (30 ± 2 days) after the last dose administration. Patients who discontinue early from the trial at the ITP visit should perform the ED assessments instead of the ITPnVn assessments. Patients who discontinue from the trial after the ITP visit should perform the ED assessments.

[e] An unscheduled (UNS) visit can occur at the request of the patient or the investigator. During the UNS visit, additional assessments as indicated in the SoA can be performed at the discretion of the investigator, depending on the reason for the UNS visit.

[f] No trial-related assessment is to be carried out before the patient has signed the informed consent form (ICF).

[g] Assessments of disease severity should be completed predose on dosing days and before any other trial-specific assessment, except for obtaining informed consent at SEB and the weight assessment, if applicable. The MG-ADL scale should be administered before the QMG scale. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America [MGFA]).

[h] Suicidal ideation and behavior will be assessed predose on dosing days via a targeted question based on the Patient Health Questionnaire item 9 (PHQ-9).

[i] The physical examination will be performed predose on dosing days. See Section 7.2.3 for an overview of the different assessments.

[j] Weight will be measured at SEB, at the EoA/ED visit, and when there is an obvious weight change compared to the last weight assessment. Height will be measured at SEB.

[k] Vital signs (supine blood pressure, heart rate, body temperature) will be performed predose on dosing days. It is recommended that the method used to measure body temperature at SEB is maintained throughout the trial for each patient.

[l] ECG will be performed predose on dosing days.

[m] Samples for clinical laboratory tests (hematology, clinical chemistry) will be collected predose on dosing days (see Appendix 3). Patients need to have fasted at least 8 hours prior to each sampling.

[n] Urine samples will be collected predose on dosing days (see Appendix 3).

[o] A urine pregnancy test will be performed predose on dosing days on the urine samples taken for urinalysis (only for women of childbearing potential, see DEFINITION OF TERMS).

[p] Samples for pharmacodynamic (PD) biomarkers will be collected predose on dosing days (see Appendix 3). Anti-AChR antibodies will be measured in AChR-Ab seropositive patients only. Anti-MuSK antibodies will be measured in MuSK-Ab seropositive patients only. Information on the AChR/MuSK-Ab serotype (seronegative or seropositive) is available from trial ARGX-113-1704.

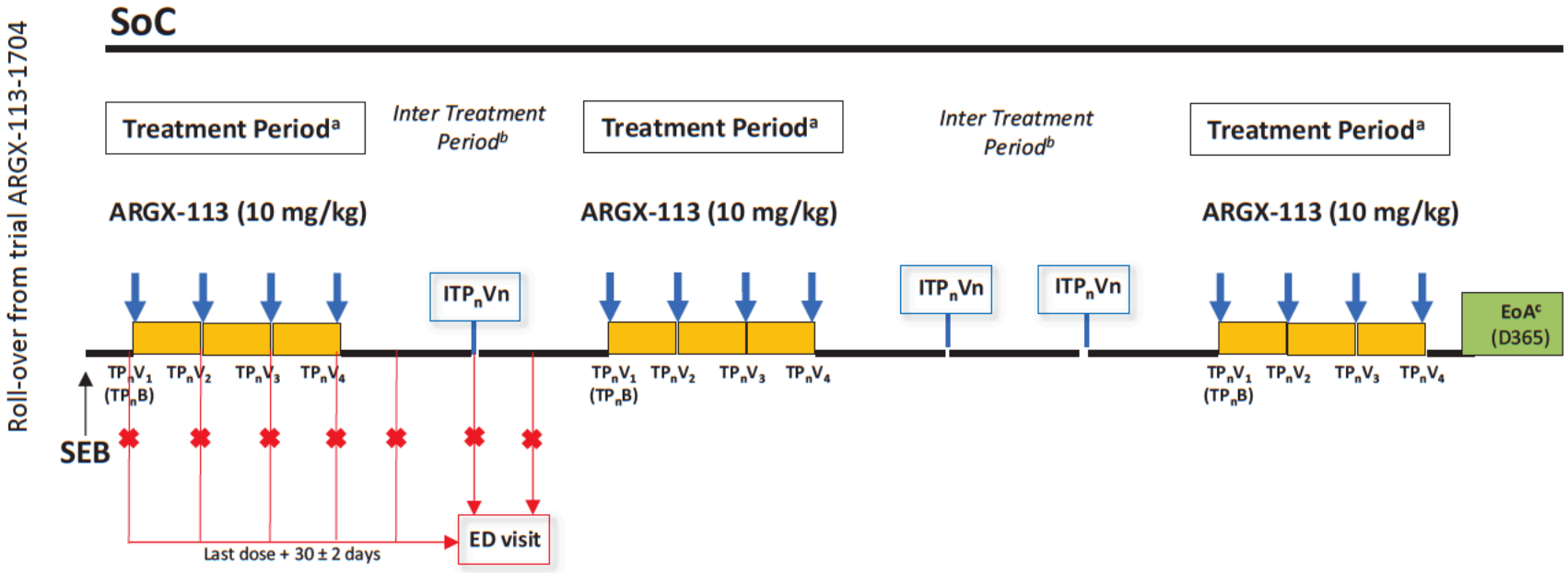
[q] Samples for anti-drug antibodies (ADAs) will be collected predose on dosing days.

[r] Efgartigimod will be administered as an intravenous (IV) infusion over a period of 1 hour at visits 1, 2, 3, and 4 of each treatment period. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring based on the patient's clinical status. At TPnV1, the conditions for (re-) treatment will be checked before administration of efgartigimod.

[s] Clinically relevant prior treatment will only be recorded at SEB. All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the trial. For vaccines where multiple doses or boosters are received, only the most recent one must be recorded.

*Assessments highlighted by use of bold italics indicate assessments that may be carried out as a telephone assessment visit under the conditions outlined in Appendix 8.

Figure 1: ARGX-113-1705 Trial Design for Part A



ED = Early Discontinuation; EoA = End of Part A; ITP$_n$Vn = Inter Treatment Period$_{(number)}$ Visit in Part A ; TP$_n$B = Treatment Period$_{(number)}$ Baseline in Part A; TP$_n$Vn = Treatment Period$_{(number)}$ Visit in Part A; SEB = Study Entry baseline; SoC = Standard of Care
Patients will be dosed on an "as needed basis".
Note: All available vaccination history will be captured as part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the trial as described in the General Schedule of Assessments for Part A (Table 1).
[a] Weekly visits (window ±1 day) during the Treatment Periods
[b] Visits every 30 days (window ±2 days) during the Inter Treatment Periods. The length between Treatment Periods may vary for each patient.
[c] EoA visit (window ± 7 days).

Table 2 General Schedule of Assessments for Part B

Assessment	Treatment Period				Intertreatment Period[a, b]	End of Study[c]/Early Discontinuation[d, e]	Unscheduled[f]
Visits Subsequent Treatment Periods	TPE_nV1[g] (TPE_nB)	TPE_nV2	TPE_nV3	TPE_nV4	$ITPE_nVn$[g]	EoS/ED	UNS
Trial Day (Visit Windows)	X	(X+7)±1	(X+14)±1	(X+21)±1			
					Y+90 (±7)	1095±7	
**MG-ADL*[h]	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Physical examination						X	X
Weight[i]	X					X	X
Vital signs[j]	X	X	X	X	X	X	X
ECG[k]	X			X	X	X	X
Clinical laboratory tests[l]	X			X		X	X
Urinalysis[m]	X			X		X	X
Urine pregnancy test[n]	X			X	X	X	X
ADA[o]	X					X	X
Efgartigimod administration[p]	X	X	X	X			
**Prior/concomitant therapy*[q]	<----------X---------->						
**Adverse events*	<----------X---------->						

ADA=anti-drug antibodies; EoS/ED=end of study/early discontinuation; ITPEV=intertreatment period visit in Part B; MG-ADL=Myasthenia Gravis Activities of Daily Living; TPEV=treatment period visit in Part B; Y=previous visit; UNS=unscheduled visit

[a] The ITPEnVn occur every 90 ±7 days after Y. The visit denominator ("n") will start at 1 at each period. At each $ITPE_nVn$, an evaluation of the need for (re-) treatment should be done prior to decide whether assessments listed for $ITPE_nVn$ or TPEnV1 are to be performed.

[b] If a patient becomes eligible for (re-)treatment with efgartigimod but cannot complete the entire treatment period within the duration of the trial, the patient should continue to the EoS visit.

[c] EoS will be up to a maximum of 3 years (1095±7 days) or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first.

[d] For patients who discontinue early from the trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4). Patients who discontinue early from the trial within a treatment period should perform the planned assessments of the corresponding treatment period visit. These patients will not receive any further administration of efgartigimod during the trial and return for the ED visit 1 month (30 ±2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the investigator. Patients who discontinue early from the trial between the last visit of a treatment period (TPE_nV4) and the next intertreatment period visit ($ITPE_nVn$) should perform the ED assessments 1 month (30 ±2 days) after the last dose administration. Patients who discontinue early from the trial at the ITPE visit should perform the ED assessments instead of the $ITPE_nVn$ assessments. Patients who discontinue prematurely from the trial after the ITPE visit should perform the ED assessments.

[e] Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002.

[f] An unscheduled (UNS) visit can occur at the request of the patient or the investigator. During the UNS visit, additional assessments as indicated in the SoA can be performed at the investigator's discretion, depending on the reason for the UNS visit.

[g] The transition to Part B can be either ITPE0Vn or TPE1V1, depending on the patient status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.

[h] Assessments of disease severity should be completed predose on dosing days and before any other trial-specific assessment, except weight, if applicable.

[i] Weight will be measured at visit 1, the EoS/ED visit, and any visit when a weight change is obvious compared to the last weight measurement.

[j] Vital signs (supine blood pressure, heart rate, body temperature) will be performed predose on dosing days. It is recommended that the method used to measure body temperature is maintained throughout the trial for each patient.

[k] A 12-lead ECG will be recorded locally. The assessments on heart rate, PR, QT, and QRS intervals will be read centrally.

[l] Samples for clinical laboratory tests (hematology, clinical chemistry) will be collected predose on dosing days, if applicable (see Appendix 3).

[m] Urine samples will be collected predose on dosing days (see Appendix 3).

[n] If a urine pregnancy test is carried out on a dosing day, then it should be performed predose (only for women of childbearing potential, see DEFINITION OF TERMS).

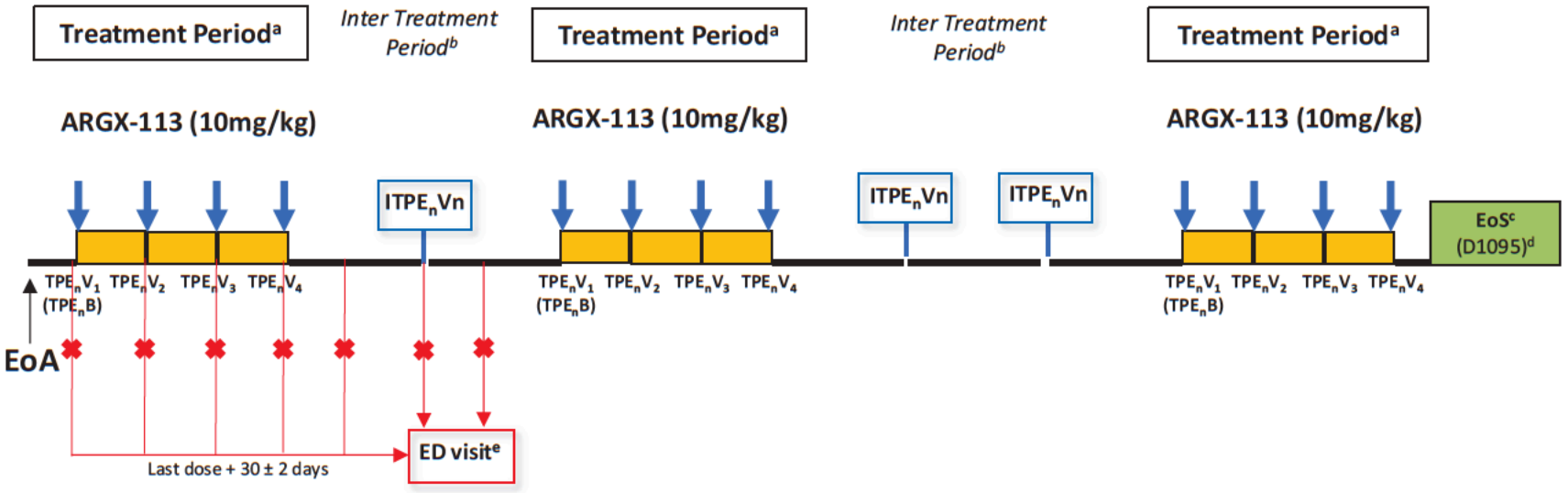
[o] Samples for anti-drug antibodies (ADAs) will be collected predose on dosing days (if applicable) and collected only in the case of early discontinuation and not at the EoS visit.

[p] Efgartigimod will be administered as an intravenous (IV) infusion over a period of 1 hour at visits 1, 2, 3, and 4 of each treatment period. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring based on the patient's clinical status. At TPE_nV1, the conditions for (re-) treatment will be checked before administration of efgartigimod.

[q] All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the trial. For vaccines where multiple doses or boosters are received, only the most recent one must be recorded.

*Assessments highlighted by use of bold italics indicate assessments that may be carried out as a telephone assessment visit under the conditions outlined in Appendix 8.

Figure 2: ARGX-113-1705 Trial Design for Part B



ED = Early Discontinuation; EoA = End of Part A; EoS = End of Study; $ITPE_nVn$ = Inter Treatment $Period_{(number)}$ Visit in Part B ; TPE_nB = Treatment $Period_{(number)}$ Baseline in Part B; TPE_nVn = Treatment $Period_{(number)}$ $Visit_{(number)}$ in Part B
Patients will be dosed on an "as needed basis".
Note: All available vaccination history will be captured as part of the participant's prior medication for vaccinations received in the past or concomitant medication for vaccinations received during the trial as described in the General Schedule of Assessments for Part A (Table 1).
[a] Weekly visits (window ±1 day) during the Treatment Periods
[b] Visits every 90 days (window ±7 days) during the Inter Treatment Periods. The length between Treatment Periods may vary for each patient.
[c] EoS visit (window ± 7 days)
[d] D1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first
[e] Patients enrolling in ARGX-113-2002 from Part B of ARGX-113-1705 must have received the previous dose of efgartigimod IV at least 30 days prior to entry into ARGX-113-2002 and must first complete the ED visit assessments from ARGX-113-1705.

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LIST OF ABBREVIATIONS

ABDEG™	antibody that enhances IgG degradation
AChE	acetylcholinesterase
AChR	acetylcholine receptor
ADA	anti-drug antibodies
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial report
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation

EDC	electronic data capture
EoA	end of Part A of the study
EoS	end of study
Fc	crystallizable fragment
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
gMG	generalized myasthenia gravis
HBV	hepatitis B virus
HCV	hepatitis C virus
HEL-ABDEG™	full-length monoclonal antibody analog of ABDEG™
HIV	human immunodeficiency virus
IB	investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin gamma
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
ITPV	intertreatment period visit in Part A
ITPEV	intertreatment period visit in Part B
IV	intravenous

IVIg	intravenous immunoglobulin
LRP4	lipoprotein receptor-related protein 4
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MuSK	muscle-specific kinase
NCI	National Cancer Institute
NSID	non-steroidal immunosuppressive drug
PD	pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire item 9
PLEX	plasma exchange
PK	pharmacokinetic(s)
QMG	Quantitative Myasthenia Gravis
SAE	serious adverse event
SEB	study entry baseline
SoC	standard of care
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TCB	treatment cycle baseline
TEAE	treatment-emergent adverse event
TPB	treatment period baseline
TPE	treatment period in Part B
TP_nB	subsequent treatment period baseline in Part A
TPE_nB	subsequent treatment period baseline in Part B

UNS	unscheduled visit
US	United States
WBC	white blood count
WHO(-DD)	World Health Organization (Drug Dictionary)

DEFINITION OF TERMS

Childbearing potential:	Women of childbearing potential are defined as all female participants unless they are postmenopausal (defined by continuous amenorrhea) for at least 2 years with a follicle-stimulating hormone (FSH) >40 IU/L or are surgically sterile (ie, who had a hysterectomy, bilateral oophorectomy, or have current documented tubal ligation or any other permanent female sterilization procedure).
Council for International Organizations of Medical Sciences (CIOMS):	The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by World Health Organization (WHO) and UNESCO in 1949. They provide a set of ethical principles regarding human experimentations, including International Reporting of Adverse Drug Reactions and International Reporting of Periodic Drug-Safety Update Summaries. The CIOMS form provides a standardized format for the reporting of suspected adverse reactions to any particular medical product and is the acceptable and widely used format for reporting suspect adverse drug reaction (ADR)/suspected unexpected serious adverse reaction (SUSAR) in clinical trials.
Contract Research Organization (CRO):	A person, or a group of persons (commercial, academic, or other), who as an independent contractor with argenx BVBA, assume(s) 1 or more obligations of argenx BVBA, eg, development of a protocol, selection and/or monitoring of investigators, evaluation of reports, preparation of materials to be submitted to Health Authorities.
Cycle	A cycle is a treatment period plus the intertreatment period.
Database Lock:	An action taken to prevent further changes to a trial database. A database is locked after review, query resolution, data cleaning and determination that it is ready for analysis.
Data Safety Monitoring Board (DSMB):	Independent group of experts that advises and whose responsibilities are to periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress and, when appropriate, efficacy and to make recommendation to the sponsor concerning the continuation, modification or termination of the trial.

Eligible:	Qualified for roll-over into the trial based upon strict adherence to inclusion/exclusion criteria.
Good Clinical Practice (GCP):	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (ICH E6).
Institutional Review Board (IRB)/Independent Ethics Committee (IEC):	An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
Informed Consent/ Informed Consent Form (ICF):	A process by which a clinical investigation participant voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a dated and signed informed consent form (ICF).
International Conference on Harmonisation (ICH):	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the 3 regions to discuss scientific and technical aspects of pharmaceutical product registration.
Investigational Medicinal Product:	A pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Protocol amendment:	A written description of a change(s) to or formal clarification of a protocol.

Treatment:	Term used throughout the clinical trial to denote a set of investigational product(s) or marketed product(s) intended to be administered to a subject.

1. INTRODUCTION

1.1. Background Information

Myasthenia gravis (MG) is an autoimmune disorder characterized in most cases by T-cell and antibody responses to neuromuscular junction proteins such as skeletal muscle nicotinic acetylcholine receptor (AChR). Antibodies against epitopes of the AChR of the neuromuscular junction cause failure of neuromuscular transmission, resulting in the characteristic fatigue and weakness associated with this severe disorder. The muscle weakness fluctuates with activity, and periods of rest offer only a temporary reprieve.[1]

Autoimmune MG has a reported worldwide prevalence of 40-180 per million people and an annual incidence of 4-12 per million people. Overall, MG incidence and prevalence shows little geographic variation.[2]

Autoimmune MG is characterized by the presence of antibodies against several components of the neuromuscular junctions. The most common antibody found in autoimmune MG is directed against post-synaptic AChRs. Anti-AChR antibodies are present in approximately 80% of all autoimmune MG patients. Less frequent autoantibodies found in autoimmune MG include the anti-muscle-specific kinase (MuSK) antibody (4% of the cases), and the anti-lipoprotein receptor-related protein 4 (LRP4) antibody (2% of the cases) directed against LRP4. All these autoantibodies belong to the immunoglobulin gamma (IgG) class.[2,3]

In approximately 5% to 20% of the MG patients, no serum antibodies against neuromuscular junction proteins can be detected.[4,5] Although in some seronegative MG patients the disease may not be mediated by antibodies, in other cases the (apparent) absence of specific autoantibodies in patients may be due to insufficient sensitivity of the assay. Indeed, one-third of MG patients, who are seronegative on standard testing, are seropositive on cell-based testing. The seronegative group probably includes some patients with anti-AChR, -MuSK or -LRP4 antibodies that are not detected because of insufficient test sensitivity.[3]

The treatment of MG is based on a variety of medications and medical procedures used either alone or in combination (see Section 1.3).

Given the pathogenic role of autoantibodies in MG, a possible novel therapeutic approach to this disease may include the use of drugs that lower the level of pathogenic autoantibodies rapidly and sustainably. Since all the specific autoantibodies found in MG belong to the IgG isotype, agents that specifically lower the level of these antibodies without affecting the level of other isotypes such as IgA, IgE and IgM may be of special interest.

One such strategy involves inhibition of the neonatal crystallizable fragment (Fc) receptor (FcRn). FcRn was shown to play a central role in trafficking IgGs and albumin into recycling pathways rescuing them from lysosomal degradation. Molecules that block the interaction of FcRn with IgGs are expected to induce degradation and fast clearance of pathogenic IgGs leading to a lowering of their serum level.[6,7]

Thus, targeting the FcRn-IgG interaction would be a rational therapeutic approach to rapidly clear pathogenic autoantibodies in IgG-driven autoimmune diseases such as MG.

1.2. Investigational Medicinal Product

Efgartigimod (ARGX-113) is a human IgG1-derived Fc fragment of the za allotype that binds with nanomolar affinity to human FcRn. Efgartigimod encompasses IgG1 residues D220-K447 (EU numbering scheme) and has been modified with the so-called ABDEG™ technology (ABDEG™ = antibody that enhances IgG degradation)[8] to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of efgartigimod at both acidic and physiological pH results in a constitutively blockage of FcRn-mediated recycling of IgGs.

Given the essential role of the FcRn receptor in IgG homeostasis, inhibiting this FcRn function, as achieved by efgartigimod, leads to rapid degradation of IgGs, which is expected to include autoantibodies in IgG-driven autoimmune diseases.

This concept has been validated in various murine disease models together with pharmacokinetic/pharmacodynamic (PK/PD) studies in cynomolgus monkeys, either by using efgartigimod or a full-lengthmonoclonal antibody analog (HEL-ABDEG™).[9,10]

The antibody clearing properties of efgartigimod were confirmed in PK/PD studies in cynomolgus monkeys. A single infusion of efgartigimod resulted in a decrease of IgG up to 55% without altering serum albumin concentrations nor IgM or IgA levels. This PD effect as measured with a tracer IgG molecule was proven to be more potent than intravenous immunoglobulin (IVIg), both in rapidity of onset as in depth of the effect. Repeated dosing could improve the PD effect up to a maximum IgG reduction of 75%.

These nonclinical data validated the further development of efgartigimod for assessing its therapeutic potential in IgG-driven autoimmune indications.

To date, a phase 1 (ARGX-113-1501) and a phase 2 (ARGX-113-1602) trial are completed as part of the clinical development of efgartigimod for the treatment of generalized myasthenia gravis (gMG).

ARGX-113-1501 was a randomized, double-blind, placebo-controlled, First-in-Human (FIH) phase 1 trial conducted in 62 healthy volunteers to assess the safety and tolerability and to evaluate the PK and PD characteristics of single and multiple ascending intravenous (IV) doses of efgartigimod. The trial showed that a single administration of efgartigimod reduced IgG levels up to 50%, while multiple dosing further lowered IgGs up to approximately 70%. IgG levels returned to baseline approximately 8 weeks following the last administration of efgartigimod. IV administration of efgartigimod at single doses up to 25 mg/kg and multiple doses of 10 mg/kg and 25 mg/kg were safe and well tolerated.

Based on an optimal PD effect combined with minimal number of observed adverse events (AEs) (compared to the 25 mg/kg dose level), the dose of 10 mg/kg once weekly for 4 weeks provided the most favorable risk-benefit profile and was therefore selected for further testing in the phase 2 trial. The outcome of the phase 2 trial indicated the efficacy and safety of 10 mg/kg in 4 weekly infusions in gMG patients

ARGX-113-1602 was a randomized, double-blind, placebo-controlled, multicenter phase 2 trial to evaluate the safety, efficacy, and PK of efgartigimod for the treatment of autoimmune MG patients with generalized muscle weakness. Eligible patients (24 in total) were randomized at a 1:1 ratio to receive efgartigimod (10 mg/kg) or placebo in 4 infusions administered 1 week apart in addition to standard of care (SoC). The clinical effect of efgartigimod was explored in this trial using validated efficacy scales commonly used in MG clinical research and practice: Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG), MGC, and MGQoL15r. The efficacy data of the 4 scales consistently point in the same direction and show a rapid onset of action, and a relevant and long-lasting clinical improvement over placebo. More specifically, on the MG-ADL scale, 75% of the patients treated with efgartigimod had a sustained clinically relevant reduction in total MG-ADL scores (defined as a reduction of at least 2 points from baseline) for a period of at least 6 consecutive weeks (starting at the latest 1 week after last infusion of investigational medicinal product [IMP]) versus 25% of patients on placebo (difference was found to be statistically significant). Furthermore, this clinical improvement observed in all scales was consistent with the observed PD data, namely a reduction of total IgG and subtypes and a decreased level of AChR autoantibodies.

The proposed phase 3 trial aims to establish the safety and tolerability of efgartigimod in class II-IVb gMG patients, and thereby validating the concept of autoantibody reduction as a therapeutic treatment modality in this indication.

This trial will be performed in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), Declaration of Helsinki, and other applicable regulatory requirements.

1.3. Standard of Care and Rationale for the Use of Efgartigimod

Several drugs and medical procedures are routinely used in the management of gMG.

Acetylcholinesterase (AChE) inhibitors are frequently used in treating MG, particularly in the mild forms of the disease. These agents include drugs such as pyridostigmine, neostigmine, and edrophonium, and their effectiveness varies widely. These drugs act by inhibiting the enzyme AChE, which is responsible for the degradation of acetylcholine. This prolongs acetylcholine exposure, which leads to an amelioration of the signs/symptoms of MG. AChE inhibitors provide a symptomatic treatment of MG and do not act on the disease's underlying pathogenic mechanism. AChE inhibitors are not efficacious in all patients with MG and can have a short duration of action, necessitating dosing several times daily.

Corticosteroids and non-steroidal immunosuppressive drugs (NSIDs) are also used in the treatment of MG. These drugs are frequently used in the more advanced stage of the disease. Corticosteroids and NSIDs are typically characterized by delayed onset of effects. Because of their multiple side effects, the lowest effective dose of corticosteroids is recommended for long-term treatment that is often indicated for chronic conditions such as MG. NSIDs are commonly used and include azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide. The use of corticosteroids and NSIDs however is associated with dose-dependent, frequent and often serious side effects whose management requires to lower the dose and to use these drugs in various combinations to find the right balance between efficacy and side effects.[2,3]

Apart from the SoC described above, new biologic agents such as rituximab and eculizumab are also used to treat specific cases of MG, such as resistant and refractory forms. However, the use of these drugs is also associated with serious and sometimes life-threatening side effects.[11,12]

Exacerbations of MG are treated using either therapeutic plasma exchange (PLEX), immunoadsorption or IVIg. In the case of PLEX, typically 1 exchange, removing 1 to 2 plasma volumes, is done every other day up to a total of 4 to 6 times, to improve muscle strength or ameliorate a myasthenic crisis. Unfortunately, this treatment is invasive and has frequent side effects such as hypotension, paresthesia, infections, and thrombotic complications. IVIg is widely used for patients with exacerbating MG. The mechanism of action of IVIg in MG is still unclear and may include interference with autoantibodies, B-cell modulation, saturation of FcRn and complement.[13,14] In addition, the use of IVIg is burdensome for the patient.

These approaches however are not always available in all clinical centers since they require specific facilities and instrumentation.[2,3]

Finally, in selected cases, surgical removal of the thymus gland is also used to ameliorate the clinical manifestations of MG. However, thymectomy is not always effective in all patients and is associated with surgery-specific risks.[2,3,15,16]

Following administration of efgartigimod (10 mg/kg) in 4 infusions administered 1 week apart in addition to SoC in patients with autoimmune MG with generalized muscle weakness in the phase 2 trial (ARGX-113-1602, also see Section 1.2), overall efgartigimod was well tolerated and demonstrated a good safety profile consistent with phase 1 data. No serious or severe AEs were reported. The following events were reported as related to efgartigimod administration: rhinorrhea, gingivitis, headache, nausea, pruritus, paresthesia, myalgia, lymphocyte count decreased, monocyte count decreased, neutrophil count decreased, contusion, feeling hot, infusion site pain and pruritus, and herpes zoster. All these events were reported as mild, except the herpes zoster, which was considered as moderate and occurred in a patient concomitantly treated with a systemic corticosteroid and NSID. Efgartigimod demonstrated a relevant and long-lasting improvement over placebo of the clinical manifestations of MG as measured by all 4 clinical efficacy MG scales, which reached statistical significance at specific timepoints on the MG-ADL, QMG, and MGQoL15r scales. Pharmacokinetic, PD, and immunogenicity profiles were consistent with phase 1 data. In addition, a potent and long-lasting reduction of AChR autoantibodies was observed.

Myasthenia gravis is considered a highly autoantibody driven disease. Efgartigimod is a highly targeted therapy postulated to result in reduced autoantibody levels. Results from the phase 2 trial indicate that it induces a strong and long-lasting improvement of the disease as measured by different efficacy scales while showing a favorable safety profile. Furthermore, this clinical improvement was consistent with the observed PD data, namely a reduction of total IgG and subtypes and a decreased level of AChR autoantibodies. Therefore, efgartigimod is believed to be a promising treatment to reduce autoantibodies in gMG patients.

1.4. Benefit-Risk Assessment

Benefits

The clinical effect of efgartigimod was explored using clinical activity tools commonly used in MG clinical research and practice: total MG-ADL, QMG, MGC, and MG-QoL15r scores. A mean total score change from baseline in total MG-ADL, QMG, MGC, and MG-QoL15r scores was observed as early as day 8 in patients treated with efgartigimod. A long-lasting reduction in total MG-ADL and MGC scores was observed, with the reduction in total scores still seen at day 78 (end of study [EoS]). Efgartigimod showed a statistically significant reduction in total MG-ADL, QMG, and MG-QoL15r scores compared with placebo at specific time points, indicating a clinical improvement in efgartigimod treatment over placebo. For all MG scales, a greater maximum mean change from baseline (reduction) was observed in the efgartigimod treatment group compared with placebo.

Eligible participants of trial ARGX-113-1704 will be offered the option to roll over to this follow-on trial where (re-)treatment of efgartigimod can be done on an "as needed basis," which is a substantial benefit for the patient.

Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration. SC administration is considered more convenient for patients than IV administration, especially if efgartigimod can be administered by the patient or caregiver at home.

Risks

No major safety findings have arisen in the ongoing and completed trials, nor any pattern of AEs which would raise concerns or alter the potential benefit-risk profile of efgartigimod.

In the phase 3 trials in patients with gMG, the majority of TEAEs were reported as mild (grade 1) or moderate (grade 2) in severity. The most frequently (≥5%) reported TEAEs during all cycles of efgartigimod 10 mg/kg treatment in the overall population who received at least 1 dose of efgartigimod were headache, nasopharyngitis, upper respiratory tract infection, diarrhea, urinary tract infection, nausea, myalgia, and oropharyngeal pain. TEAEs of severity of grade ≥3 that occurred in >2 patients who received efgartigimod were headache and myasthenia gravis. The only TEAE that led to efgartigimod discontinuation reported in >2 patients was myasthenia gravis. No SAEs were assessed by the investigator as related to efgartigimod treatment.

Four fatal cases have been reported, however, none of the fatal events were assessed by the investigator as related to efgartigimod treatment. Causes of death was unknown in a patient who died at home without witness. The other 3 patients died due to myasthenia gravis crisis, lung cancer Stage IV, and acute myocardial infarction. These 4 patients were between 55 and 79 years old and all had clear comorbidities, including underlying gMG.

Adverse drug reactions were identified based on safety data from the phase 3 double-blind, placebo-controlled trial in patients with gMG and include upper respiratory tract infection, urinary tract infection, bronchitis, myalgia, and procedural headache.

Due to the efgartigimod mechanism of action of reducing IgG levels, AEs in the Infections and Infestations SOC have been defined as AESIs. In the Phase 3 trials with efgartigimod IV in patients with gMG, the most frequently reported treatment-emergent AESIs by preferred term

(PT) were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and bronchitis. Most AESIs were mild or moderate in severity. Few patients had severe or serious AESIs reported, and no SAEs of AESIs were assessed by the investigator as related to efgartigimod treatment.

All therapeutic proteins have the potential to elicit immune responses, potentially resulting in hypersensitivity or allergic reactions. As with any IV injection, the potential exists for infusion-related reactions (IRRs) to occur during or within 48 hours following the administration of efgartigimod. Overall, the frequency of IRRs in the clinical trials was low. At the PT level, no TEAEs of drug hypersensitivity or anaphylactic reaction were reported. None of the IRRs reported were serious. Most IRRs were mild in severity and no IRRs resulted in a change in efgartigimod administration. For administration of efgartigimod PH20 SC, the local injection site will be monitored during the trial.

In the Phase 3 trial with efgartigimod IV in patients with gMG, no differences or imbalances were observed between the efgartigimod and placebo groups in the incidence or rates of abnormal values in clinical laboratory parameters. There was no reduction in levels of serum albumin with the administration of efgartigimod. In the extension trial in patients with gMG, the most frequently reported grade ≥3 abnormalities were lymphocyte count decreased.

No clinically significant changes in vital signs and/or electrocardiogram (ECG) findings have been observed in clinical trials to date.

Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women.

In summary, efgartigimod has been well tolerated in clinical trials conducted to date.

Please refer to the current investigator's brochure (IB) for a full safety and efficacy summary.

An independent Data Safety Monitoring Board (DSMB) is responsible for ongoing safety monitoring during the trial and will meet on a regular basis (see Section 7.2.6).

Considering the efficacy and safety data collected up to date and the design of the trial that has appropriate measures to ensure safe trial participation, which minimizes the risk to patients participating in this trial, the potential risks identified in association with efgartigimod are justified by the potential benefits gained by patients receiving efgartigimod.

2. TRIAL OBJECTIVES

2.1. Primary Objective

To evaluate the long-term safety and tolerability of efgartigimod in acetylcholine receptor antibody (AChR-Ab) seropositive patients.

2.2. Secondary Objective

To evaluate the long-term safety and tolerability of efgartigimod in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

2.3. Tertiary Objectives

Part A only:

- To evaluate the disease severity as assessed by total MG-ADL score changes in AChR-Ab seropositive patients.
- To evaluate the disease severity as assessed by total MG-ADL score changes in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).
- To evaluate disease severity as assessed by total QMG score changes in AChR-Ab seropositive patients.
- To evaluate disease severity as assessed by total QMG score changes in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).
- To evaluate the effect of efgartigimod on PD (total IgG, IgG subtypes, autoantibodies [anti-AChR antibodies and anti-MuSK antibodies]).

Part A and B:

- To evaluate the immunogenicity of efgartigimod.

3. TRIAL ENDPOINTS

3.1. Primary Endpoint

Incidence and severity of AEs, serious adverse events (SAEs), vital signs, ECG and laboratory assessments over the duration of the trial in AChR-Ab seropositive patients.

3.2. Secondary Endpoint

Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments over the duration of the trial in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients).

3.3. Tertiary Endpoints

Part A only:

- Total MG-ADL score changes compared to the treatment period baseline of the first cycle (TP_1B) and the corresponding TP_nB in AChR-Ab seropositive patients.
- Total MG-ADL score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Total QMG score changes compared to TP_1B and the corresponding TP_nB in AChR-Ab seropositive patients.
- Total QMG score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Percentage decrease (compared to TP_1B and the corresponding TP_nB) of total IgG level and IgG subtypes in efgartigimod (re-)treated patients.
- Percentage decrease (compared to TP_1B and the corresponding TP_nB) of autoantibodies (anti-AChR antibodies and anti-MuSK antibodies) in efgartigimod (re-)treated patients.

Part A and B:

- Incidence and prevalence of anti-drug antibodies (ADA) to efgartigimod.

4. INVESTIGATIONAL PLAN

4.1. Summary of Trial Design

Methodology

DESCRIPTION

This is a 3-year (maximum), single-arm, open-label, multicenter, phase 3 follow-on trial of ARGX-113-1704 to evaluate the long-term safety and tolerability of efgartigimod in patients with gMG. The trial consists of 2 parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first. The additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension will also enable additional long-term safety and tolerability data to be collected.

A variable number of treatment periods consisting of 4 weekly infusions of efgartigimod (10 mg/kg of body weight) infused over a period of 3 weeks will be administered to eligible patients on an "as needed basis" on top of their SoC. The time between treatment periods is based on the duration of the treatment effect and may vary from patient to patient and within each patient from period to period (patient-tailored approach).

The first visit of trial ARGX-113-1705 will coincide with the last visit of trial ARGX-113-1704 for each patient.

The SEB will be set at the first trial visit, while the baseline of each subsequent treatment period (TP_nB for Part A or TPE_nB for Part B) will be set at visit 1 of each corresponding treatment period.

ROLL-OVER

At the EoS visit of trial ARGX-113-1704, eligible patients will be offered the option to roll over into this trial. Patients in need of (re-)treatment in trial ARGX-113-1704 but who cannot complete a Treatment Cycle within the time frame of that trial, may immediately roll over to this trial to receive treatment with efgartigimod.

Patients who discontinued early from trial ARGX-113-1704 or discontinued early from randomized treatment for rescue or pregnancy reasons or for an SAE that is likely to result in a life-threatening situation or pose a serious safety risk in that trial will not be offered the option to roll over into this trial.

Patients who discontinued early from randomized treatment for other reasons and patients who had a temporary interruption from randomized treatment in trial ARGX-113-1704 may be offered the option to roll over into this trial.

Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration.

Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002.

Patients can enroll in ARGX-113-2002 until recruitment for this study is closed. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.

(RE-)TREATMENT (Part A)

Each patient will start a (new) treatment period with efgartigimod when all of the following criteria are met:

- The patient has completed the previous treatment period (ie, after visit 4)
- The patient has a total MG-ADL score of ≥5 points with more than 50% of the total score due to non-ocular symptoms
- The patient has a reduction in the total MG-ADL score of <2 points compared to the score at:
    1. The last treatment cycle baseline (TCB) in trial ARGX-113-1704 for the first treatment period (TP_1) in trial ARGX-113-1705
    2. The last treatment period Baseline (TP_nB) for all subsequent treatment periods (TP_{n+1}) in trial ARGX-113-1705

However, patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. Patients who require an additional treatment but who are not eligible to receive (re-)treatment for the reasons listed here will remain in the trial to receive appropriate alternative MG treatment (see Appendix 5 and Appendix 6).

Patients who have a treatment failure to efgartigimod for 3 consecutive treatment periods will be discontinued from the trial. Treatment failure means the absence of a decrease of at least 2 points in total MG-ADL score compared to the corresponding TP_nB in at least 50% of the assessments (ie, TP_nV2, TP_nV3, TP_nV4, and the first posttreatment period visit).

If a patient becomes eligible for (re-)treatment with efgartigimod by meeting the criteria for the total MG-ADL score as stated in Section 4.1, but cannot complete the entire treatment period during Part A (ie, after day 336) then the patient can be transitioned to Part B after completing the end of Part A (EoA) visit assessments (Table 1). These assessments should be completed even if the patient is unwilling or unable to continue to Part B.

The transition to Part B can be either at $ITPE_0Vn$ or TPE_1V1, depending on the patient status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.

(RE-)TREATMENT (Part B)

If the patient feels that his/her condition has deteriorated, then the investigator may start a new treatment period at an intertreatment period (ITPE) visit or the patient may contact the investigator to attend an unscheduled visit.

A patient can start the next treatment period and receive efgartigimod if all of the following criteria are met:

- The patient has completed the previous treatment period (ie, after visit 4)*
- The investigator determines that the patient will benefit from re-treatment
- There is at least 1 calendar month (minimum 4 weeks) between treatment periods (ie, between TPE_nV4 and $TPE_{n+1}V1$)

*A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions in Section 4.4.1 are met.

However, patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk.

If a patient becomes eligible for (re-)treatment with efgartigimod but cannot complete the entire treatment period within the duration of the trial, the patient should continue to the EoS visit.

If the investigator considers that the patient will not have a clinical benefit from (re-)treatment then the patient cannot start a new treatment period. The patient should then continue to the EoS visit.

STANDARD OF CARE (SoC)

In Part A:

Permitted SoC for MG treatment under this protocol include NSIDs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as acetylcholinesterase (AChE) inhibitors.

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed:

- From trial entry until 1 week after the last infusion of the first treatment period.
- From the first infusion until 1 week after the last infusion of each subsequent treatment period.

From 1 week after the last infusion of each treatment period up to and prior to the administration of the first infusion of the next treatment period, a dose reduction in SoC consistent with current medical practice is allowed.

In case these medications are taken for another indication than MG, same conditions apply.

Administration of AChE inhibitors must be halted for at least 12 hours prior to performing the QMG assessment. Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC.

In Part B:

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice.

PLEX, intravenous immunoglobulin (IVIg), immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.

TIME BETWEEN TREATMENT PERIODS

At the end of each treatment period, patients will enter a variable intertreatment period during which they will be treated with their SoC only. The length of the intertreatment period may vary from patient to patient and for each patient from period to period (patient-tailored approach). For Part A, the visit frequency in the Intertreatment period is every 30 days (± 2 days) after the previous visit. For Part B, the visit frequency in the intertreatment period is every 90 days (± 7 days) after the previous visit. If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then the EoA visit should be performed instead.

RESCUE THERAPY (Part A only)

Rescue therapy will be limited to PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination. Rescue therapy is permitted for patients experiencing protocol-defined MG clinical deterioration AND if in addition the treating physician believes that the patient's health is in jeopardy if rescue therapy is not given. An MG clinical deterioration permitting rescue therapy to be given is defined as a patient experiencing at least 1 of the following: (1) new or worsening of respiratory / bulbar symptoms or (2) at least 2-point increase of individual non-ocular MG-ADL items. Whenever possible, prior to giving rescue therapy to a patient, the Medical Director at the sponsor and the Medical Monitor at the sponsor's designated contract research organization (CRO) should be informed.

In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from the trial.

EARLY DISCONTINUATION

For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4, Figure 1, and Figure 2).

Patients who discontinue early from the trial within a treatment period should perform the planned assessments of the corresponding treatment period visit. These patients will not receive any further administration of efgartigimod during the trial and will return for the ED visit 1 month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the investigator.

Patients who discontinue early from the trial between the last visit of a treatment period (TP_nV4 or TPE_nV4) and the next intertreatment period visit (ITP_nVn or $ITPE_nVn$) should perform the ED assessments 1 month (30 ± 2 days) after the last dose administration.

Patients who discontinue early from the trial at the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments instead of the ITP_nVn (Part A) or $ITPE_nVn$ (Part B) assessments.

Patients who discontinue early from the trial after the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments.

Any patient prematurely discontinuing the trial during Part A should perform the EoA/ED assessments according to the General Schedule of Assessments for Part A (Table 1). Any patient prematurely discontinuing the trial during Part B should perform the EoS/ED assessments for Part B (Table 2).

Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.

TEMPORARY INTERRUPTION FROM TRIAL TREATMENT

A patient who does not need to be discontinued early from the trial might still have a temporary interruption from trial treatment, which is defined as discontinuation only from the current treatment period. Therefore, these patients might still be eligible for further additional treatments with efgartigimod within this trial.

Patients for whom treatment is interrupted will have to complete the current treatment period and will continue the trial as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2) but without drug administration. A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions mentioned above are met.

A schematic of the trial design is presented in Figure 1 for Part A and in Figure 2 for Part B.

4.2. Discussion of Trial Design

In the current trial, efgartigimod will be administered in patients with gMG, with the aim to evaluate the long-term safety and tolerability of efgartigimod.

This trial is designed as a 3-year (maximum), single-arm, open-label, follow-on trial of ARGX-113-1704. The trial consists of 2 parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first. The additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension will also enable additional long-term safety and tolerability data to be collected.

Patients who have completed at least 1 cycle of treatment and at least 1 year of trial ARGX-113-1705 and have started Part B are eligible to enroll in the open-label trial ARGX-113-2002 to receive efgartigimod by SC administration.

With the exception of patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from trial treatment for rescue or pregnancy reasons or an SAE that is likely to result in a life-threatening situation or pose a serious safety risk, all participants of trial ARGX-113-1704 who reached the EoS visit are allowed to roll over into this trial.

The first visit of trial ARGX-113-1705 will coincide with the last visit of trial ARGX-113-1704 for each patient.

In the same way, with the exception of patients who discontinued early from Part A of this trial, all participants of Part A who reached the EoA visit can be transitioned to Part B of this trial.

The first visit of Part B of this trial will coincide with the last visit of Part A for each patient.

Efgartigimod will be administered to eligible patients on an "as needed basis" on top of their SoC in treatment periods. This SoC serves as a rational therapeutic approach for IgG-mediated immune diseases such as MG by targeting the FcRn-IgG interaction and alleviating autoimmune disease symptoms by rapidly clearing pathogenic autoantibodies. The time between treatment periods is based on the duration of the treatment effect and may vary from patient to patient and within each patient from period to period (patient-tailored approach).

In Part A, a change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed from trial entry until 1 week after the last infusion of the first treatment period, and from the first infusion until 1 week after the last infusion of each subsequent treatment period. From 1 week after the last infusion of each Treatment Period up to and prior to the administration of the first infusion of the next treatment period, a dose reduction in SoC consistent with current medical practice is allowed.

In Part B, a change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed without restrictions, following current medical practice.

PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.

The chosen primary and secondary endpoints in this trial are to evaluate the long-term safety and tolerability of efgartigimod over the duration of the trial, as well as by cycle, in AChR-Ab seropositive patients and in the overall population (AChR-Ab seropositive and seronegative patients).

Both MG AChR-Ab seropositive as well as MG AChR-Ab seronegative patients will be included in the trial. AChR-Ab seronegative patients are patients in which AChR-Ab cannot be detected in serum using routine laboratory methods. However, there is evidence that in these seronegative patients, MG is also driven by other autoantibodies of the Ig class, such as MuSK, LRP4 or by other so far unidentified autoantibodies to other antigens of the neuromuscular junction. In addition, in other cases, the absence of AChR-Ab may be due to the insufficient sensitivity of the routine assays which are unable to detect low affinity autoantibodies. Therefore, given the mechanism of action of efgartigimod and the IgG pathogenesis of MG in most of the so-called seronegative patients, there is reason to believe that, similarly to the AChR-Ab seropositive

patients, AChR-Ab seronegative patients will also benefit from treatment with efgartigimod. The dose regimen selected for this trial is the same as in trial ARGX-113-1704.

The choice of the dose/regimen of efgartigimod (4 weekly infusions of 10 mg/kg) was made because, as observed in a phase 1 trial in human volunteers, it causes a marked and long-lasting decrease of IgG level believed to be related to efficacy with only few mild AEs. In the same trial, higher doses did not result in significant further reductions of IgG while, at the same time, the number of subjects experiencing efgartigimod-related AEs increased. On the other hand, a lower dose of 2 mg/kg resulted in substantially less reduction of IgG concentrations (2.3-fold difference in maximum IgG decrease). As suggested by the PK/PD modeling, lower doses (eg, 5 mg/kg) will result in a less marked decrease of the IgG level and therefore may result in a less pronounced therapeutic effect. In addition, in a phase 2 trial (ARGX-113-1602) in patients with gMG, the dose/regimen chosen for the current trial induced a clinically meaningful improvement on the MG-ADL and QMG scales and, at the same time, confirming the acceptable safety profile of the drug. Therefore, the dose of 10 mg/kg of efgartigimod administered weekly for 4 weeks seems to provide the best benefit/risk ratio and was selected for future trials.

All safety and disease severity assessments used in this trial are standard, ie, widely used and generally recognized as reliable, accurate, and relevant.

4.3. Selection of Trial Population

4.3.1. Inclusion Criteria

Patients will roll over in this trial only if they meet **all** of the following criteria:

1. Patients with the ability to understand the requirements of the trial, provide written informed consent, and can comply with the trial protocol procedures.
2. Patients who participated in trial ARGX-113-1704 and are eligible for roll over, ie:

– Patients who reached EoS at day 182 in trial ARGX-113-1704.

– Patients who need (re-)treatment in trial ARGX-113-1704 but cannot complete a Treatment Cycle within the time frame of that trial may immediately roll over into this trial to receive treatment with efgartigimod.

– Patients who discontinued early from randomized treatment for other reasons than pregnancy, rescue therapy or an (S)AE in trial ARGX-113-1704 may be offered the option to roll over into this trial.

– Patients who had a temporary interruption from randomized treatment in trial ARGX-113-1704 may be offered the option to roll over into this trial.

3. Patients are required to be on a stable dose of their MG treatment (SoC) prior to SEB. The SoC is limited to AChE inhibitors, steroids and NSIDs (eg, azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide).

Note: AChE inhibitors must be withheld for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America (MGFA), before the QMG assessment.

4.3.2. Exclusion Criteria

Patients will not roll over in this trial if they meet **any** of the following criteria:

1. Patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from randomized treatment for pregnancy or rescue reasons or an SAE that is likely to result in a life-threatening situation or pose a serious safety risk.
2. Pregnant and lactating women, and those intending to become pregnant during the trial or within 90 days after the last dosing. Women of childbearing potential (DEFINITION OF TERMS) should have a negative urine pregnancy test at SEB. The contraceptive requirements for women of childbearing potential are described in Appendix 8:Temporary Changes to Study Procedures in ARGX-113-1705 Related to the COVID-19 Pandemic

Introduction

As the COVID-19 pandemic poses issues for both sites and patients and presents unprecedented challenges in uncharted territory, this crisis prompted the sponsor to perform a critical review of both efgartigimod administration and changes needed to the study in order to safeguard patient safety, while still being able to gather additional data.

The risk/benefit, safety profile, guidance for site conduct in terms of visits and assessments, as well as data entry, and potential changes in the Schedule of Assessments are included below.

Safety of Efgartigimod: Mechanism of Action, Pharmacodynamics and Risk/Benefit in Patient Safety

Efgartigimod administration results in a targeted reduction in levels of all IgG subtypes. However, and more importantly, it does not impact levels of other immunoglobulin isotypes, such as IgA and IgM. Other elements of the immune system are not impacted by efgartigimod treatment.

Efgartigimod induces a targeted reduction of IgG levels, without impacting IgG production. The maximum mean reduction in total IgG is approximately 70%; therefore, residual IgG and other immunoglobulin levels remain constant during treatment. It is therefore anticipated that patients can mount an immune response. In support of this, experiments in FcRn knockout animals and in animals treated with FcRn antagonist demonstrated that a specific immune response was obtained following an antigen trigger, albeit with reduced (antigen-specific) IgG titers. Additionally, after ceasing efgartigimod treatment, IgG recycling returns and total IgG levels increase and return to baseline levels within a few weeks.

Looking at administration in humans, efgartigimod treatment at doses ≥10 mg/kg have been administered to more than 120 healthy volunteers and patients with generalized myasthenia

gravis (gMG), immune thrombocytopenia, and pemphigus in studies carried out prior to phase 3 studies. No general or infection-related safety concerns were identified.

The phase 3 ADAPT gMG study enrolled 167 patients and data will be available in mid-2020. An active assessment of adverse event reports during the study remains ongoing. Although the phase 3 ADAPT data are blinded, no safety concern has been identified to date.

Available data from trials of other FcRn antagonists have not identified any increased risk of infection.

ADAPT/ADAPT+: Pre-existing Safety Measures and Changes to Be Implemented in the Current Situation

The phase 3 ADAPT study implements multiple layers of safety measures and reporting. Efgartigimod is administered in treatment cycles, in which 4-weekly infusions are followed by additional treatment cycles that are administered according to clinical need. Therefore, during the follow-up period after each treatment cycle, FcRn recycling resumes and IgG levels begin to increase.

The protocol gives guidance to temporarily or permanently discontinue treatment when the patient has signs of clinically significant of bacterial, viral, or fungal infection, in order to treat the underlying condition. The treatment can be initiated at a later time once the clinically significant infection has been deemed resolved. A Treatment Period can be considered as interrupted if the patient is not able to visit the site for more than 1 visit. In such cases, a new Treatment Period can be initiated at a later date.

Additionally, any case of infection is regarded as an adverse event of special interest (AESI) and is subject to structured safety reporting with standardized questions in the eCRF.

The current COVID-19 situation warrants new measures to be introduced for patient safety. These measures will allow patients to be evaluated remotely if/when quarantine is imposed. For example, any remaining visits in an interrupted Treatment Period, may be performed remotely, in cases where the patient is not allowed or cannot physically visit the site. These measures respect both patient safety and local guidance, as well as allowing basic safety data to be collected.

The assessments identified for telephone assessment visits are highlighted with the use of bold italics in the existing Schedule of Assessments for Part A in Table 1 and for Part B in Table 2. Guidance on the execution of these visits and assessments is given below.

By providing a structured back-up plan, we aim to mitigate the risks of the COVID-19 pandemic, while still respecting both patient safety and collection of safety data and remaining compliant with GCP.

Visits with the possibility of remote assessment by telephone:

TP_xV2, TPE_xV2, TP_xV3, TPE_xV3, TP_xV4, TPE_xV4, ITP_xVx, $ITPE_xVx$, EoA, EoS, ED, and UNS. See the Schedule of Assessments for Part A (Table 1) and for Part B (Table 2).

Treatment Period visits will be replaced by telephone assessment visits during the current COVID-19 situation when the Treatment Period is considered interrupted.

Mandatory physical visits:

Initiating a new Treatment Period can only be done when the patient is physically on site.

Guidance to Sites in Case of Suspected COVID-19 in Patients

As sponsor we want to emphasize and highlight the need to follow the guidance issued by local authorities. Wherever guidance is unclear, or if no specific guidance is available, argenx will recommend to either postpone the visit if possible or evaluate the need for telephone assessments to replace a physical visit.

The site should contact the patient prior to each visit, and conduct the following COVID-19 assessments:

1. Does the patient have symptoms, such as cough, fever, muscle pain, shortness of breath*?

- If NO: Go to Questions 2 and 3.

- If YES:

• The patient should be tested for COVID-19:

The investigator needs to document a positive COVID-19 test as an AESI. The anonymized result needs to be sent to the sponsor for filing. If COVID-19 safety measures are stopped according to local regulations, COVID-19 tests should continue to be performed and the results sent to the sponsor.

*Shortness of breath includes an otherwise unexplained deterioration in the patient's MG-ADL score for breathing. In cases where the MG-ADL score for breathing is 2 or 3 additional COVID-19 testing should be carried out. The exception to this is when a patient has an MG-ADL score for breathing of 2 at baseline. In such cases the patient should only be tested when the MG-ADL score for breathing returns to 2 after previous improvement or when it deteriorates to 3.

The visit will only take place once the patient has a negative test for COVID-19. The planned visit may need to be rescheduled or **can be replaced by a telephone assessment visit**. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **Remaining visits in the Treatment Period can be performed as telephone assessment visits.**

• If the patient is tested and found to be COVID-19 negative:

The patient can come to the next visit as scheduled. Follow-up of the patient should be done according to the protocol (decision to be taken if treatment can be given or is to be postponed).

• If the patient is tested and found to be COVID-19 positive:

The patient can only come to the site once he/she has a negative test for COVID-19, and so the planned visit may need to be rescheduled or replaced by a telephone assessment visit. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **The remaining visits in the Treatment Period can be replaced by telephone assessment visits.**

2. The patient has no Corona-like symptoms and is not aware of any contact he/she may have had with someone who tested positive for COVID-19:
• The visit can proceed as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

3. The patient has no Corona-like symptoms but has been in contact with someone who tested positive for Corona virus:

• If the contact was 14 days or longer before the study visit => the visit can go ahead as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

• If the contact was less than 14 days before the study visit => the visit needs to be rescheduled at least 14 days after the contact occurred or be replaced by a telephone assessment visit.

How to: Information related to study procedures and data collection

The assessments deemed suitable for telephone consultation are:

- Re-consenting where warranted, MG-ADL, Adverse Event and Concomitant Medication questioning.

Since QMG needs quantification by the physician, using specific equipment, such as a dynamometer and spirometer, this assessment is not deemed suitable for telephone assessment.

Telephone consultation will allow safety data to be collected and to check on the patient's well-being, while the derived MG-ADL score may give an indication of the need for another treatment with efgartigimod.

Re-consenting with the updated ICF, or consent to Part B of the ADAPT+ study can be done remotely in view of the COVID-19 situation.

Options for consent might entail:

- physical signature by sending the ICF to the patient by courier and having a phone call with the patient, then having the signed document sent back to the site.
- phone call with the patient, asking for email confirmation to corroborate verbal consent.
- organize a conference call or video call together with the patient and impartial witness, where needed.
- if no phone call or video call is possible, email documented consent.

Depending on regional requirements the options can be limited, after consultation with the relevant IRB/IEC and/or regulatory authority.

Data collected during a telephone assessment visit can be entered into the e-CRF pages of the corresponding "missed" visit. Enter the date of the phone call as the "date of visit" and enter the

data obtained in the applicable CRF pages. For the assessments that are not performed, answer "no" to the question if the assessment was made in the respective forms. Add "COVID-19 telephone" in the comment section of the CRF.

If you are not able to contact the patient, inactivate the full study visit in the CRF and confirm the missing visit in the comments section as "COVID-19."

Other than conducting telephone assessments, there may be other changes in the current practice on site. Halting spirometry in COVID-19 patients may be required, or only allowing use of a dedicated spirometry device (for contamination reasons). There can be a temporary halt in performing this assessment, or conducting a partial assessment is also permitted.

In order to give a clear overview of protocol deviations related to the specific COVID-19 situation, dedicated protocol deviations with the COVID-19 label have been created to which any missed visit or assessment can be attributed.

3. APPENDIX 9.
4. Male patients who are sexually active and do not intend to use effective methods of contraception (as mentioned above) during the trial or within 90 days after the last dosing or male patients who plan to donate sperm during the trial or within 90 days after the last dosing. The contraceptive requirements for male patients are described in Appendix 8: Temporary Changes to Study Procedures in ARGX-113-1705 Related to the COVID-19 Pandemic

Introduction

As the COVID-19 pandemic poses issues for both sites and patients and presents unprecedented challenges in uncharted territory, this crisis prompted the sponsor to perform a critical review of both efgartigimod administration and changes needed to the study in order to safeguard patient safety, while still being able to gather additional data.

The risk/benefit, safety profile, guidance for site conduct in terms of visits and assessments, as well as data entry, and potential changes in the Schedule of Assessments are included below.

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Efgartigimod administration results in a targeted reduction in levels of all IgG subtypes. However, and more importantly, it does not impact levels of other immunoglobulin isotypes, such as IgA and IgM. Other elements of the immune system are not impacted by efgartigimod treatment.

Efgartigimod induces a targeted reduction of IgG levels, without impacting IgG production. The maximum mean reduction in total IgG is approximately 70%; therefore, residual IgG and other immunoglobulin levels remain constant during treatment. It is therefore anticipated that patients can mount an immune response. In support of this, experiments in FcRn knockout animals and in animals treated with FcRn antagonist demonstrated that a specific immune response was obtained following an antigen trigger, albeit with reduced (antigen-specific) IgG titers.

Additionally, after ceasing efgartigimod treatment, IgG recycling returns and total IgG levels increase and return to baseline levels within a few weeks.

Looking at administration in humans, efgartigimod treatment at doses ≥10 mg/kg have been administered to more than 120 healthy volunteers and patients with generalized myasthenia gravis (gMG), immune thrombocytopenia, and pemphigus in studies carried out prior to phase 3 studies. No general or infection-related safety concerns were identified.

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Available data from trials of other FcRn antagonists have not identified any increased risk of infection.

ADAPT/ADAPT+: Pre-existing Safety Measures and Changes to Be Implemented in the Current Situation

The phase 3 ADAPT study implements multiple layers of safety measures and reporting. Efgartigimod is administered in treatment cycles, in which 4-weekly infusions are followed by additional treatment cycles that are administered according to clinical need. Therefore, during the follow-up period after each treatment cycle, FcRn recycling resumes and IgG levels begin to increase.

The protocol gives guidance to temporarily or permanently discontinue treatment when the patient has signs of clinically significant of bacterial, viral, or fungal infection, in order to treat the underlying condition. The treatment can be initiated at a later time once the clinically significant infection has been deemed resolved. A Treatment Period can be considered as interrupted if the patient is not able to visit the site for more than 1 visit. In such cases, a new Treatment Period can be initiated at a later date.

Additionally, any case of infection is regarded as an adverse event of special interest (AESI) and is subject to structured safety reporting with standardized questions in the eCRF.

The current COVID-19 situation warrants new measures to be introduced for patient safety. These measures will allow patients to be evaluated remotely if/when quarantine is imposed. For example, any remaining visits in an interrupted Treatment Period, may be performed remotely, in cases where the patient is not allowed or cannot physically visit the site. These measures respect both patient safety and local guidance, as well as allowing basic safety data to be collected.

The assessments identified for telephone assessment visits are highlighted with the use of bold italics in the existing Schedule of Assessments for Part A in Table 1 and for Part B in Table 2. Guidance on the execution of these visits and assessments is given below.

By providing a structured back-up plan, we aim to mitigate the risks of the COVID-19 pandemic, while still respecting both patient safety and collection of safety data and remaining compliant with GCP.

Visits with the possibility of remote assessment by telephone:

TP_xV2, TPE_xV2, TP_xV3, TPE_xV3, TP_xV4, TPE_xV4, ITP_xVx, $ITPE_xVx$, EoA, EoS, ED, and UNS. See the Schedule of Assessments for Part A (Table 1) and for Part B (Table 2).

Treatment Period visits will be replaced by telephone assessment visits during the current COVID-19 situation when the Treatment Period is considered interrupted.

Mandatory physical visits:

Initiating a new Treatment Period can only be done when the patient is physically on site.

Guidance to Sites in Case of Suspected COVID-19 in Patients

As sponsor we want to emphasize and highlight the need to follow the guidance issued by local authorities. Wherever guidance is unclear, or if no specific guidance is available, argenx will recommend to either postpone the visit if possible or evaluate the need for telephone assessments to replace a physical visit.

The site should contact the patient prior to each visit, and conduct the following COVID-19 assessments:

1. Does the patient have symptoms, such as cough, fever, muscle pain, shortness of breath*?

- If NO: Go to Questions 2 and 3.

- If YES:

• The patient should be tested for COVID-19:

The investigator needs to document a positive COVID-19 test as an AESI. The anonymized result needs to be sent to the sponsor for filing. If COVID-19 safety measures are stopped according to local regulations, COVID-19 tests should continue to be performed and the results sent to the sponsor.

*Shortness of breath includes an otherwise unexplained deterioration in the patient's MG-ADL score for breathing. In cases where the MG-ADL score for breathing is 2 or 3 additional COVID-19 testing should be carried out. The exception to this is when a patient has an MG-ADL score for breathing of 2 at baseline. In such cases the patient should only be tested when the MG-ADL score for breathing returns to 2 after previous improvement or when it deteriorates to 3.

The visit will only take place once the patient has a negative test for COVID-19. The planned visit may need to be rescheduled or **can be replaced by a telephone assessment visit**. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **Remaining visits in the Treatment Period can be performed as telephone assessment visits.**

• If the patient is tested and found to be COVID-19 negative:

The patient can come to the next visit as scheduled. Follow-up of the patient should be done according to the protocol (decision to be taken if treatment can be given or is to be postponed).

• If the patient is tested and found to be COVID-19 positive:

The patient can only come to the site once he/she has a negative test for COVID-19, and so the planned visit may need to be rescheduled or replaced by a telephone assessment visit. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **The remaining visits in the Treatment Period can be replaced by telephone assessment visits.**

2. The patient has no Corona-like symptoms and is not aware of any contact he/she may have had with someone who tested positive for COVID-19:

• The visit can proceed as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

3. The patient has no Corona-like symptoms but has been in contact with someone who tested positive for Corona virus:

• If the contact was 14 days or longer before the study visit => the visit can go ahead as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

• If the contact was less than 14 days before the study visit => the visit needs to be rescheduled at least 14 days after the contact occurred or be replaced by a telephone assessment visit.

How to: Information related to study procedures and data collection

The assessments deemed suitable for telephone consultation are:

- Re-consenting where warranted, MG-ADL, Adverse Event and Concomitant Medication questioning.

Since QMG needs quantification by the physician, using specific equipment, such as a dynamometer and spirometer, this assessment is not deemed suitable for telephone assessment.

Telephone consultation will allow safety data to be collected and to check on the patient's well-being, while the derived MG-ADL score may give an indication of the need for another treatment with efgartigimod.

Re-consenting with the updated ICF, or consent to Part B of the ADAPT+ study can be done remotely in view of the COVID-19 situation.

Options for consent might entail:

- physical signature by sending the ICF to the patient by courier and having a phone call with the patient, then having the signed document sent back to the site.

- phone call with the patient, asking for email confirmation to corroborate verbal consent.
- organize a conference call or video call together with the patient and impartial witness, where needed.
- if no phone call or video call is possible, email documented consent.

Depending on regional requirements the options can be limited, after consultation with the relevant IRB/IEC and/or regulatory authority.

Data collected during a telephone assessment visit can be entered into the e-CRF pages of the corresponding "missed" visit. Enter the date of the phone call as the "date of visit" and enter the data obtained in the applicable CRF pages. For the assessments that are not performed, answer "no" to the question if the assessment was made in the respective forms. Add "COVID-19 telephone" in the comment section of the CRF.

If you are not able to contact the patient, inactivate the full study visit in the CRF and confirm the missing visit in the comments section as "COVID-19."

Other than conducting telephone assessments, there may be other changes in the current practice on site. Halting spirometry in COVID-19 patients may be required, or only allowing use of a dedicated spirometry device (for contamination reasons). There can be a temporary halt in performing this assessment, or conducting a partial assessment is also permitted.

In order to give a clear overview of protocol deviations related to the specific COVID-19 situation, dedicated protocol deviations with the COVID-19 label have been created to which any missed visit or assessment can be attributed.

5. APPENDIX 9.
6. Patients with known hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) seropositivity.
7. Patients with known autoimmune disease other than MG (for example autoimmune thyroiditis, rheumatoid arthritis…) that would interfere with an accurate assessment of clinical symptoms.
8. Patients with clinical evidence of other significant disease or patients who underwent a recent major surgery, which could confound the results of the trial or put the patient at undue risk. Patients with renal/hepatic function impairment can be included.
9. Patients with known medical history of hypersensitivity to any of the ingredients of efgartigimod or placebo.

4.4. Early Discontinuation

The criteria for roll-over into this trial (see Section 4.3) are to be followed explicitly. If it is noted that a patient who does not meet 1 or more of the inclusion and/or meets 1 or more of the

exclusion criteria is inadvertently rolled over, the Medical Monitor at sponsor's designated CRO and the sponsor's Medical Director must be contacted immediately.

Early discontinuation from the trial is defined as the permanent cessation of further participation in the trial prior to its planned completion.

Patients **must** be discontinued early from the trial if:

- They withdraw their consent.
- The investigator, after discussion with the sponsor's Medical Director, deems it is in the patient's best interest.
- Patient is pregnant.
- Patient receives rescue therapy (Part A only).
- Patient develops an SAE that is likely to result in a life-threatening situation or pose a serious safety risk to the patient.
- Prohibited medication is taken (Part A only) (see Section 6.8.1).

Patients **might** discontinue early from the trial if:

- Patient has clinical evidence of bacterial, viral or fungal disease or any other significant disease which could confound the results of the trial or put the patient at undue risk. In this situation, decision on whether or not to discontinue patients early from trial will depend on the evaluation on a case-by-case basis. Patients who, after evaluation of the above situations are not discontinued from the trial, may have a temporary interruption from trial treatment (see Section 4.4.1).

For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4, Figure 1, and Figure 2).

Patients who discontinue early from the trial within a treatment period should perform the planned assessments of the corresponding treatment period visit. These patients will not receive any further administration of efgartigimod during the trial and will return for the ED visit 1 month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the investigator.

Patients who discontinue early from the trial between the last visit of a treatment period (TP_nV4 or TPE_nV4) and the next intertreatment period visit (ITP_nVn or $ITPE_nVn$) should perform the ED assessments 1 month (30 ± 2 days) after the last dose administration.

Patients who discontinue early from the trial at the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments, instead of the ITP_nVn (Part A) or $ITPE_nVn$ (Part B) assessments.

Patients who discontinue early from the trial after the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments.

Any patient prematurely discontinuing the trial during Part A should perform the EoA/ED assessments according to the General Schedule of Assessments for Part A (Table 1). Any patient prematurely discontinuing the trial during Part B should perform the EoS/ED assessments according to the General Schedule of Assessments for Part B (Table 2).

All patients are free to withdraw consent from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice to further treatment. Prior to actual withdrawal of consent, an effort should be made to perform a final set of assessments as per the EoA/ED visit in the General Schedule of Assessments for Part A (Table 1) or the EoS/ED visit in the General Schedule of Assessments for Part B (Table 2). Investigators will make and document all efforts made to contact those patients who do not return for scheduled visits.

Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705.

The reason for early discontinuation from the trial must be documented by the investigator on the appropriate page of the eCRF.

4.4.1. Temporary Interruption From Trial Treatment

A patient who does not need to be discontinued early from the trial might still have a temporary interruption from trial treatment. A temporary interruption from trial treatment is defined as a discontinuation only from the current treatment period, but the patient might still be eligible for further additional treatments with efgartigimod within this trial.

Patients for whom treatment is interrupted will have to complete the current treatment period and will continue the trial as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions mentioned above are met.

4.4.2. Missed Doses

Patients who miss 1, 2, or 3 infusions per treatment period will stay in the trial and will follow the assessments as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). These patients may be eligible for further treatment periods during the trial. A patient who has missed doses in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions in Section 4.4.1 are met.

4.5. Protocol Deviations

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

Planned protocol exemptions or waivers will not be approved by the sponsor.

4.6. Early Termination of Trial or Site

The trial may be terminated at any time by the sponsor for safety concerns due to SAEs, inability to achieve the recruitment target within reasonable time or if in the sponsor's judgment, there are no further benefits to be expected from the trial. In such a case, the sponsor or delegate will inform the trial investigators, institutions, and all regulatory authorities.

The trial can also be terminated by the Regulatory Authority for any reason or if recommended by the DSMB, or at a site level by the IRB/IEC. The sponsor may close individual trial sites prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of patients.

4.7. End of Trial Definition

The end of trial is defined as last patient last visit.

5. TRIAL PROCEDURES

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. When a protocol-required procedure cannot be performed, the investigator will document the reason and any corrective and preventive actions that he/she has taken to ensure that the normal processes are adhered to in source documents. The trial team should be informed of these incidents in a timely manner.

Patients should be seen for all visits on the designated days or as closely as possible to the original planned visit schedule. There is a permissible window of ±1 day for treatment period visits (visit 1 to visit 4), of ±2 days for ITP_nVn (Part A), and of ±7 days for the $ITPE_nVn$ (Part B), EoA visit (day 365) and the EoS visit (day 1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). Every effort should be made to schedule every visit on the exact day (which is relative to the baseline visit [SEB, TP_nB or TPE_nB]) within the window as described in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2).

Each treatment period consists of 4 weekly infusions over a period of 3 weeks.

The SEB will be set at the first trial visit, while the baseline of each subsequent treatment period (TP_nB or TPE_nB) will be set at visit 1 of each corresponding treatment period.

At all visits, assessments of disease severity should be performed first, before any other trial-specific assessments, with the only exception of obtaining informed consent at SEB and the weight assessment. The MG-ADL scale needs to be performed prior to the QMG scale (Part A) as per Table 1. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment (Part A).

As from signature of informed consent until last study visit, all AEs that occur and all concomitant medications, whether allowed or not, that are taken during the trial are to be recorded on the appropriate pages in the electronic case report form (eCRF).

5.1. Informed Consent and Roll-Over Visit

The roll-over visit (SEB) can be either ITP_0V1 or TP_1V1, depending on the patient status regarding the need for (re-)treatment upon roll-over from trial ARGX-113-1704. The first visit in trial ARGX-113-1705 will always coincide with the last visit in trial ARGX-113-1704.

The patient must sign the informed consent form (ICF) prior to any trial-related assessment. The assessments done for the last visit in trial ARGX-113-1704 should not be repeated.

Prior to signing the ICF, trial patients will be instructed not to participate in any other clinical trial that involves an intervention or collection of data until the completion of the current trial.

After informed consent has been obtained, participants of trial ARGX-113-1704 will be screened at the site for eligibility to roll over to this trial based on the inclusion and exclusion criteria defined in Sections 4.3.1 and 4.3.2, respectively.

In addition to obtaining written informed consent and the eligibility check, the following assessments will be performed at SEB:

- Clinically relevant medical and surgical history, clinically relevant prior treatments and all concomitant medications (see Sections 6.8 and 7.2.5)
- Demographic characteristics (date of birth, sex, race, and ethnicity, per national regulations)
- Assessments of disease severity – the MG-ADL scale should be administered before the QMG scale
- Suicidal ideation and behavior will be assessed via a targeted question based on the Patient Health Questionnaire item 9 (PHQ-9)[17]
- Complete physical examination, including at a minimum: general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological systems
- Weight and height
- Vital signs (supine blood pressure, heart rate, body temperature). It is recommended that the method used to measure body temperature at SEB is maintained throughout the trial for each patient
- ECG (heart rate, PR, QT, and QRS interval)
- Clinical laboratory tests (see Appendix 3 for an overview of the clinical laboratory tests that will be assessed). Patients need to have fasted at least 8 hours prior to sampling
- Urinalysis
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)
- Pharmacodynamic biomarkers (anti-AChR antibodies in AChR-Ab seropositive patients only, total IgG and subtypes [IgG1, IgG2, IgG3 and IgG4], and anti-MuSK antibodies in MuSK-Ab seropositive patients only). Information on the AChR/MuSK-Ab serotype (seronegative or seropositive) is available from trial ARGX-113-1704
- Anti-drug antibodies (ADA)
- Assess AEs, if any

5.2. Treatment Period

5.2.1. Treatment Period Part A

A treatment period will include assessments in 4 weekly visits including treatment with efgartigimod in eligible patients in need for (re-)treatment. A new treatment period can only be started if it can be completed within the 1-year duration of Part A of the trial (re-treatment in Part A can start at the latest on day 336). Otherwise, the patient can be transitioned to Part B after completing the EoA visit assessments (Table 1). These assessments should be completed

even if the patient is unwilling or unable to continue to Part B, then he/she should continue to the EoA visit.

The following assessments will be performed from visit 1 to visit 4 of each treatment period:

- Assessments of disease severity – the MG-ADL scale should be administered before the QMG scale*
- Suicidality assessment*
- Physical examination*
- Weight will only be measured in case there is an obvious weight change compared to the last weight assessment*
- Vital signs*
- ECG, only at visit 1 and visit 4 of each treatment period*
- Clinical laboratory tests. Patients need to have fasted at least 8 hours prior to sampling*
- Urinalysis*
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)*
- Pharmacodynamic biomarkers (anti-AChR antibodies in AChR-Ab seropositive patients only, total IgG and subtypes [IgG1, IgG2, IgG3 and IgG4], and anti-MuSK antibodies in MuSK-Ab seropositive patients only)*
- ADA, only at visit 1 and visit 4 of each treatment period*
- Administration of efgartigimod as an IV infusion over a period of 1 hour. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring, based on the patient's clinical status
- Review of concomitant medication and rescue therapy
- Assess AEs, if any

*These assessments should be performed prior to administration of efgartigimod (predose).

At visit 1 of each subsequent treatment period, the conditions for (re-)treatment will be checked before administration of efgartigimod (see Section 4.1).

Patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. Patients who are in need of an additional treatment but who are not eligible to receive (re-)treatment for reasons listed here will remain in the trial to receive appropriate alternative MG treatment.

Patients who fail to respond to efgartigimod for 3 consecutive treatment periods will be discontinued from the trial. Treatment failure means the absence of a decrease of at least 2 points in total MG-ADL score compared to the corresponding TP_nB in at least 50% of the assessments (ie, TP_nV2, TP_nV3, TP_nV4 and the first posttreatment period visit).

If a patient becomes eligible for (re-)treatment with efgartigimod by meeting the criteria for the total MG-ADL score as stated in Section 4.1, but cannot complete the entire treatment period during Part A (ie, after day 336) then the patient can be transitioned to Part B after completing the EoA visit assessments in Table 1. These assessments should be completed even if the patient is unwilling or unable to continue to Part B (see Section 5.1).

The transition to Part B can be either $ITPE_0Vn$ or TPE_1V1, depending on the patient status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed from trial entry until 1 week after the last infusion of the first Treatment Period, and from the first infusion until 1 week after the last infusion of each subsequent Treatment Period.

From 1 week after the last infusion of each Treatment Period up to and prior to the administration of the first infusion of the next Treatment Period, a dose reduction in SoC consistent with current medical practice is allowed.

5.2.2. Treatment Period Part B

A Treatment Period will include assessments in 4 weekly visits including treatment with efgartigimod in eligible patients in need for (re-)treatment. A new Treatment Period can only be started if it can be completed within the trial duration (up to maximum 3 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first).

The following assessments will be performed from visit 1 to visit 4 of each Treatment Period:

- Assessments of disease severity (MG-ADL scale)*
- Weight will be measured at visit 1 and when there is an obvious weight change compared to the last weight assessment*
- Vital signs*
- ECG, only at visit 1 and visit 4 of each Treatment Period*
- Clinical laboratory tests (local labs), only at visit 1 and visit 4 of each Treatment Period.*
- Urinalysis, only at visit 1 and visit 4 of each Treatment Period*
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS), only at visit 1 and visit 4 of each Treatment Period*
- ADA, only at visit 1 of each Treatment Period*
- Administration of efgartigimod as an IV infusion over a period of 1 hour. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring, based on the patient's clinical status
- Review of concomitant medication

- Assess AEs if any

*These assessments should be performed prior to administration of efgartigimod (predose).

At visit 1 of each Treatment Period, the conditions for (re-)treatment will be checked before administration of efgartigimod (see Section 4.1).

Patients may not receive (re-)treatment with efgartigimod if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk.

If a patient becomes eligible for (re-)treatment with efgartigimod but cannot complete the entire Treatment Period within duration of the trial, the patient should continue to the EoS visit.

If the investigator considers that the patient will not have a clinical benefit from re-treatment then the patient cannot start a new Treatment Period. The patient should then continue to the EoS visit.

A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice.

5.3. Intertreatment Period

Intertreatment period visits occur every 30 days after the previous visit in Part A and every 90 days after the previous visit in Part B.

At each ITP_nVn (Part A) or $ITPE_nVn$ (Part B) an evaluation of the need for (re-)treatment should be done. In case the patient is not in need of (re-)treatment, assessments for ITP_nVn (Part A) or $ITPE_nVn$ (Part B) should be performed as listed below and per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). However, in case the evaluation shows that the patient is in need of (re-)treatment and is also eligible for (re-)treatment, the assessments according to TP_nV1 (Part A) or TPE_nV1 (Part B) are to be performed instead (see Section 5.2). If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then the EoA visit should be performed instead.

The following assessments will be performed in Part A:

- Assessments of disease severity – the MG-ADL scale should be administered before the QMG scale
- Suicidality assessment
- Physical examination
- Weight will only be measured in case there is an obvious weight change compared to the last weight assessment
- Vital signs
- ECG
- Clinical laboratory tests. Patients need to be fasted at least 8 hours prior to sampling
- Urinalysis

- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)
- Pharmacodynamic biomarkers (anti-AChR antibodies in AChR-Ab seropositive patients only, total IgG and subtypes [IgG1, IgG2, IgG3 and IgG4], and anti-MuSK antibodies in MuSK-Ab seropositive patients only)
- Review of concomitant medication and rescue therapy
- Assess AEs, if any

The following assessments will be performed in Part B:

- Assessments of disease severity (MG-ADL scale)
- Vital signs
- ECG
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)
- Review of concomitant medication
- Assess AEs, if any

5.4. End of Part A, End of Study, and Early Discontinuation Visit

In case of early discontinuation, the same assessments as scheduled for EoA (day 365) or EoS (day 1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first) must be performed as follows:

For EoA/ED (Part A):

- Assessments of disease severity – the MG-ADL scale should be administered before the QMG scale and before any other assessments except for weight
- Suicidality assessment
- Physical examination
- Weight
- Vital signs
- ECG
- Clinical laboratory tests – Patients should have fasted at least 8 hours before sampling
- Urinalysis
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)
- Pharmacodynamic biomarkers (anti-AChR antibodies in AChR-Ab seropositive patients only, total IgG and subtypes [IgG1, IgG2, IgG3, and IgG4], and anti-MuSK antibodies in MuSK-Ab seropositive patients only)

- ADA
- Review of concomitant medication and rescue therapy
- Assess AEs if any

For EoS/ED (Part B):

- Before enrolling in ARGX-113-2002 from Part B, patients must first complete the early discontinuation (ED) visit assessments specified in Table 2. The previous efgartigimod IV dose must have been received at least 30 days before entry into ARGX-113-2002. Patients who enroll in ARGX-113-2002 will not return to ARGX-113-1705
- Assessments of disease severity (MG-ADL scale) should be administered before any other assessments except weight
- Physical examination
- Weight
- Vital signs
- ECG
- Clinical laboratory tests (local labs)
- Urinalysis
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS)
- ADA (only in case of ED)
- Review of concomitant medication
- Assess AEs, if any

5.5. Unscheduled Visit

It is at the investigator's discretion or at patient's request to initiate an unscheduled (UNS) visit, if deemed necessary for the patient's safety and well-being. All such visits will be documented in the eCRF with any additional required documentation based on the nature of UNS visit.

6. TRIAL TREATMENT

6.1. Treatment Administered

Only patients who need (re-)treatment with efgartigimod, provided they are eligible (see Section 4.1 for the criteria for [re-]treatment), will be treated with efgartigimod.

Efgartigimod will be administered weekly for 3 weeks (4 infusions) as an IV infusion (total volume of 125 mL and a dose of 10 mg/kg of body weight) at visits 1, 2, 3 and 4 of each Treatment Period. A variation of ± 10% of the amount, as planned per protocol, of efgartigimod administered to the patient will not be considered an overdose/underdose. In case of a significant (>10%) change in body weight, the dose will be recalculated.

Although efgartigimod was administered over a period of 2 hours in all the other clinical trials conducted so far, in this trial, for patient's convenience and because no safety concerns are anticipated based on observations in the other trials, efgartigimod will be administered over a period of 1 hour. Please refer also to the IB, Section 6.3.

Details on infusion rate and time will be given in the IMP management manual (pharmacy manual).

6.2. Identity of Investigational Medicinal Product

Efgartigimod will be supplied to the investigator or designated site staff at the investigational site, by and under the responsibility of the sponsor's designated IMP supply vendor, who will also provide the investigator with certificate of analysis, certificate of conformity and European Union Qualified Person (EU QP) release documents.

Efgartigimod will be provided as a sterile, colorless, clear concentrate for solution for IV administration in a formulation of [redacted]. The concentration of efgartigimod will be 20 mg/mL presented in a 20R vial. The extractable volume from 1 vial is 20 mL. Appropriate dilutions in a 0.9% saline solution will be made on site prior to administration.

Efgartigimod will be manufactured in accordance with Good Manufacturing Practice (GMP) regulations. Detailed instructions on efgartigimod management on site (including preparation) will be included in the IMP management manual (pharmacy manual).

The dose will be 10 mg/kg (total dose per efgartigimod infusion is capped at 1200 mg for patients with body weight ≥120 kg).

6.3. Packaging and Labeling

Efgartigimod will be labeled and secondary packed in accordance to local laws and regulatory requirements.

6.4. Storage of Investigational Medicinal Product

The investigator (or his/her designee) is responsible for the correct and safe storage of efgartigimod assigned to the clinical site, in a locked, secure storage facility with access limited

to those individuals authorized to dispense efgartigimod, and maintained within the appropriate temperature ranges. efgartigimod must be stored as specified at delivery and in the original packaging.

Efgartigimod must be stored refrigerated (2-8°C or 35-46°F) in their secondary packaging, should not be exposed to freezing temperatures, should not be shaken and should be protected from direct sunlight during storage at the clinical site.

Further requirements on temperature logging during storage and information on how to handle temperature excursions can be found in the IMP management manual (pharmacy manual).

6.5. Method of Assigning Patients to Treatment Group

Not applicable.

6.6. Timing of Dose for Each Patient

Only to patients who need (re-)treatment, efgartigimod will be administered IV over a period of 1 hour as 4 weekly infusions at visits 1, 2, 3, and 4 of each Treatment Period, provided they are eligible. Patients will be asked to remain at the site for a minimum of 1 hour after the end of infusion as part of routine safety monitoring at visits 1, 2, 3, and 4 of each Treatment Period.

6.7. Blinding

This is an open-label trial with a single treatment group; no blinding will be applied.

6.8. Prior Treatments and Concomitant Medications

Clinically relevant prior treatments received by the patient including (1) previous MG treatments (including SoC) with patient's response and reason for changing treatment/dose in the last 12 months and (2) non-MG treatment in the last 6 months, prior to Screening in trial ARGX-113-1704. Information should include start and stop dates and tick box for those continuing as concomitant medication.

Vaccines (except for live/live-attenuated vaccines) will be allowed during the trial when administered at least 48 hours pre-infusion or 48 hours post-infusion of IMP.

Any vaccination received within 28 days of screening up until 28 days after the final dose of the IMP should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration.

All concomitant medications whether allowed or not must be recorded in the eCRF.

6.8.1. Prohibited Medications During the Trial

The following medications or treatments will lead to discontinuation from treatment during Part A of the trial as from SEB onwards:

- Any IgG therapy
- A change in the type or an increase of the dose/frequency of SoC, even if used for indications other than MG

- Any monoclonal antibody for immunomodulation
- Live/live-attenuated vaccines
- Rescue therapy when used in patients who meet the criteria to be rescued
- Use of PLEX or immunoadsorption more than once during study period

In Part B of the trial, a change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed without restrictions, following standard clinical practice.

PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.

6.8.2. Rescue Therapy (Part A only)

Rescue therapy is permitted for patients experiencing protocol-defined MG clinical deterioration AND if in addition the treating physician believes that the patient's health is in jeopardy if rescue therapy is not given. An MG clinical deterioration permitting rescue therapy to be given is defined as a patient experiencing at least 1 of the following: (1) new or worsening of respiratory / bulbar symptoms or (2) at least 2-point increase of individual non-ocular MG-ADL items.

Rescue therapy will be limited to PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination. The type of rescue therapy used should be documented.

In case a patient needs rescue therapy according to the treating investigator, the Medical Director at the sponsor should be informed in addition to the Medical Monitor at the sponsor's designated CRO; whenever possible prior to actual implementation of the rescue therapy.

In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from the trial.

6.9. Medical Care of Patients After End of Study

After a patient has completed the trial, or has withdrawn/discontinued early, usual treatment will be administered, if required, in accordance with the trial site's SoC and generally accepted medical practice depending on the patient's individual needs. The sponsor will not provide any additional care to these patients.

6.10. Treatment Compliance

The investigator should promote treatment compliance by stating that compliance is necessary for the patient's safety and the validity of the trial. The prescribed dose, timing, and mode of administration may not be changed. All dates and start and end time of efgartigimod administration and any deviations from the intended regimen must be recorded.

6.11. Handling Missed Doses of Investigational Medicinal Product

Patients in need for (re-)treatment will receive 4 weekly IV infusions of efgartigimod at a dose of 10 mg/kg over a period of 1 hour during each Treatment Period, provided they are eligible.

All efforts will be done to ensure that the patient receives the 4 administrations of efgartigimod within the allowed time windows. However, if a patient misses 1 or more doses in any Treatment Period, the patient will not be discontinued from the trial or from further trial treatment and will complete all further visits and assessments according to the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2). This patient may be eligible for further Treatment Periods during the trial.

In case a dose needs to be delayed for more than 3 days, the dosing should be skipped to ensure 2 consecutive doses are given with an interval of at least 3 days.

6.12. Accountability of Investigational Medicinal Product

Detailed instructions on accountability of efgartigimod will be included in the IMP management manual (pharmacy manual).

6.13. Storage of Blood Samples in the Trial

Any remaining samples after the analysis per protocol has been completed may be stored for up to 15 years for future additional research to address any scientific questions related to efgartigimod or MG, unless this would not be allowed according to local regulations or the patient would not agree.

7. TRIAL ASSESSMENTS

7.1. Monitoring of Disease Severity

Monitoring of disease severity will be assessed using MG-ADL (Part A and B) and QMG (Part A only). The assessments, where applicable, have to be performed predose on all efgartigimod infusion days and prior to any other assessment at each visit, except for the assessment of weight (if applicable) and signing of the ICF at SEB. The MG-ADL scale needs to be performed prior to the QMG scale in Part A (Table 1).

Monitoring of disease severity for a given patient is preferentially assessed, whenever possible, by 1 and the same trained evaluator throughout the course of the trial.

7.1.1. Myasthenia Gravis Activities of Daily Living

The MG-ADL is an 8-item patient-reported scale (Appendix 1) to assess MG symptoms and their effects on daily activities. It evaluates the capacity to perform different activities of daily living such as talking, chewing, swallowing, breathing, brushing the teeth/combing the hair, or rising from a chair and it also assesses double vision and eyelid droop. It is a discrete quantitative variable in which the 8 items are rated from 0 to 3 and the total score can point from 0 to 24, with higher total scores indicating more impairment. The assessments to be performed using MG-ADL (Appendix 1) do not require any equipment to assess MG symptoms and their effects on daily activities. The scoring of MG-ADL should be performed by a trained and certified evaluator.

7.1.2. Quantitative Myasthenia Gravis

The QMG quantifies disease severity based on impairments of body functions and structures as defined by the International Classification of Functioning, Disability and Health.[18]

The QMG consists of 13 items (Appendix 2) that assess ocular, bulbar, and limb function. Out of the 13 items, 6 are timed tests of endurance measured in seconds. Each item has a possible score from 0-3. The total possible score is 39, where higher total scores indicate more severe impairments. It is based on quantitative testing of specific muscle groups to assess limb function. It requires minimal equipment such as spirometer, mouthpieces that fit the spirometer, nose clips, stopwatch, cups and water for swallowing tests, goniometer, dynamometer, and is based on the trained rater's examination. The scoring of QMG should be performed by a trained evaluator.

7.2. Safety

Safety assessments will consist of monitoring and recording all AEs, pregnancies, suicidality assessment (Part A only), safety laboratory testing, measurement of vital signs, ECGs, physical examinations; and other tests that are deemed critical to the safety evaluation of the trial in all patients who receive at least 1 dose of efgartigimod. As discussed in Section 7.2.1.5, any pregnancy that occurs while a patient is enrolled into the trial will also be monitored and reported according to the appropriate regulations.

The DSMB will evaluate the safety data periodically (see Section 7.2.6).

7.2.1. Adverse Events

The investigator is responsible for recording all AEs observed during the trial from the time the patient signs the ICF until the last contact of the patient.

Definition of AE: An AE is any untoward medical occurrence in a clinical trial patient whether or not a pharmaceutical product is administered, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or efgartigimod, whether or not considered related to the medicinal product or efgartigimod.

An AE can also be a new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), if considered clinically relevant by the investigator.

Abnormal laboratory values, or test results, physical examination findings, and other abnormal investigational findings (ie, ECG) should not be reported as AEs unless they are considered clinically significant, eg, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support) or lead to treatment discontinuation.

Death is not considered an AE but an outcome.

MG disease worsening, if considered clinically relevant by the investigator, can be reported as AE, provided that it is supported by a clinically relevant change in total MG-ADL score (as compared to SEB). The investigator should contact the sponsor in case of clinically relevant worsening of the disease.

Adverse Drug Reaction (ADR): Any untoward and unintended response in a patient to efgartigimod, which is related to any dose administered to that patient.

Definition of Serious AE (SAE): An SAE, experience or reaction, is any untoward medical occurrence (whether considered to be related to efgartigimod or not) that at any dose:

- Results in death
- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization. However, a planned hospitalization related to the administration of efgartigimod is not considered an SAE

  (Hospital admissions and/or surgical operations planned before a trial are not considered SAEs or if the illness or disease, which caused hospitalization, existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected way during the trial. However, the condition for which the surgery is required may be an AE.)
- Results in persistent or significant disability or incapacity, OR
- Is a congenital abnormality or birth defect

- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in inpatient hospitalization

Suspected Unexpected Serious Adverse Reactions (SUSARs) and Unexpected Adverse Reactions: Any suspected adverse reaction that is serious, unexpected, and considered to be related to drug exposure is defined as a SUSAR.

An unexpected AE is any adverse drug event, which is not listed in the current IB or is not listed at the specificity or intensity that has been observed.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

An untoward and unintended post-dosing response to a non-trial drug is, by definition, not a SUSAR, but is, however, an AE.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to efgartigimod or trial procedures. The action taken with the investigational drug and the outcome of the event must also be recorded.

Treatment-emergent adverse event (TEAE): Any AE temporally associated with the use of efgartigimod, whether considered related to efgartigimod or not. TEAEs are recorded from the start of efgartigimod administration, until completion of the patient's last visit.

Overdose

For the purposes of this trial, exceeding the dosage requirements specified in this protocol (see Section 6.1) represents an overdose. In case of suspected overdose, the patient should be treated according to standard medical practice based on the investigator's judgment.

Severity

All AEs observed will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The NCI-CTCAE is a descriptive terminology, which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. 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. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on 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 non-invasive intervention indicated; limiting age--appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Relationship

The causal relationship between efgartigimod/trial procedures and the AE has to be characterized as unrelated, unlikely, related, possible, and probable.

- Events can be classified as "unrelated" if there is not a reasonable possibility that efgartigimod caused the AE.
- An "unlikely" relationship suggests that only a remote connection exists between efgartigimod and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.
- A "related" relationship suggests that the AE follows a reasonable temporal sequence from administration of efgartigimod, it follows a known or expected response pattern to efgartigimod and it cannot reasonably be explained by known characteristics of patient's clinical state.
- A "possible" relationship suggests that the association of the AE with efgartigimod is unknown; however, the AE is not reasonably supported by other conditions.
- A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.

In final evaluation for reporting, the relationship will be converted into "Binary Determination" as per Council for International Organizations of Medical Sciences (CIOMS). Unrelated and Unlikely will be clubbed into "Unrelated" and Related, Possible and Probable will be clubbed into "Related" for final reporting purpose.

7.2.1.1. Adverse Events of Special Interest

An AESI (serious or non-serious, related or not related) is an event of scientific and medical concern specific to the sponsor's product or program.

Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with the low IgG levels. As such, any infection will be considered AESI in this trial. Further characterizing information will be collected in the eCRF, such as: location of infection, relationship to underlying condition, medical history and concomitant medication, reoccurrence of previous infection, previous rescue therapy, any confirmatory procedure, culture or urgent medical intervention.

7.2.1.2. Reporting of Adverse Events and Serious Adverse Events

All AEs that occur during the trial from signature of the ICF until the last study visit are to be recorded on the appropriate AE pages (either "serious" or "non-serious") in the eCRF. The

investigator should complete all the details requested, including dates of onset, time of onset, stop date (when applicable), stop time (when applicable), severity, action taken, outcome, and relationship to efgartigimod, and to trial procedures. Each event should be recorded separately in the eCRF.

All AEs spontaneously reported by the patient or reported in response to the open question from the trial personnel: "*Have you had any health problems since the previous visit or since you were last asked?*," or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Any SAE, including death due to any cause, which occurs during this trial after signature of the ICF, whether or not related to efgartigimod, must be reported immediately (within 24 hours of the trial site's knowledge of the event). All SAEs will be recorded (within 24 hours) on the paper SAE Report Form and the AE form in the eCRF, the investigator or delegated site staff should check that all entered data are consistent. An alert email for the SAE report in the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the electronic data capture (EDC) system. The paper SAE Report Form should be faxed or emailed to the sponsor's designated CRO (see the Safety Mailbox/Fax details on the title page of this protocol).

The report will contain as much available information concerning the SAE to enable the sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. These timelines apply to initial reports of SAEs and to all follow-up reports.

Criteria for documenting the relationship to efgartigimod, as well as severity, outcome, and action taken will be the same as those previously described.

The investigator shall report within 24 hours any SAE (s)he becomes aware of after a patient's last visit if a causal relationship with the investigational product is suspected. Such a serious adverse reaction (SAR) is to be collected and reported as previously described for SAEs.

All SAEs that are spontaneously reported within 30 days after the last trial visit are to be collected and reported as previously described and all efforts should be made to follow-up until resolution.

Additional follow-up information should be completed and entered on a paper SAE Report Form and sent by fax/email to the sponsor's designated CRO.

7.2.1.3. Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

The sponsor's designee will be responsible for reporting all SUSARs, the Analysis of Similar Events (AOSE), and any other applicable reports to regulatory authorities, ethics committees, and investigators, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor's designee will also prepare an expedited report for other safety issues where applicable.

The investigational site will also forward a copy of all expedited reports to his or her IEC/IRB in accordance with national regulations.

7.2.1.4. Follow-up of Adverse Events and Serious Adverse Events

Any AEs observed from signing the ICF to the last study visit will be followed up to resolution, until the patient is lost to follow-up, or until the patient withdraws consent. Resolution means that the patient has returned to a baseline state of health or the investigator does not expect any further improvement or worsening of the AE.

Every effort should be made to follow all (S)AEs considered to be related to efgartigimod or trial procedures until an outcome can be reported. If the patient is lost to follow-up, all AEs will be categorized based on the investigator's last assessment.

All SAEs that are spontaneously reported after the last study visit are to be collected and reported as previously described (as per Section 7.2.1.2) and will be followed up. During the trial period, resolution of SAEs (with dates) should be documented on the SAE page of the eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to the baseline status or stabilization cannot be established, an explanation should be recorded on the SAE page of the eCRF.

All pregnancies reported during the trial should be followed until pregnancy outcome.

For SAEs, non-serious AEs, and pregnancies, the sponsor's designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

7.2.1.5. Reporting and Follow-up Requirements for Pregnancies

7.2.1.5.1. Pregnancies in Female Patients

Urine pregnancy tests will be conducted and analyzed locally at visits as detailed in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2). Results will be recorded in the eCRF.

If a patient becomes pregnant after the administration of efgartigimod and up to 90 days after the patient received the last infusion, the sponsor and/or sponsor's designee should be informed immediately (ie, within 24 hours of the trial site's knowledge of the event). The following actions will be performed:

- The patient should immediately be discontinued from trial treatment.
- The patient should have the planned ED assessments.
- All planned assessments (see Sections 4.4 and 5.4) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the patient withdraws informed consent.

The investigator must update the patient with information currently known about potential risks and about available treatment alternatives. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or

absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

If required by local regulations, the female participant will be requested to sign a separate pregnancy ICF. Full details will be recorded on a paper Pregnancy Report Form and submitted via email or fax (see the Safety Mailbox/Fax details on the title page of this protocol), and reporting details will be specified in the trial manual. The investigator will update the Pregnancy Report Form with additional information as soon as the outcome of the pregnancy is known.

If the outcome of the pregnancy is an SAE, then this must be additionally reported as an SAE on the appropriate SAE Report Form.

7.2.1.5.2. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the trial or up to 90 days after they received the last infusion of efgartigimod. A Pregnancy Report Form should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via email or fax (see the Safety Mailbox/Fax details on the title page of this protocol). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to efgartigimod.

The pregnant partner will need to sign an ICF to allow for follow-up on her pregnancy. Once the ICF has been signed, the investigator will update the Pregnancy Report Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.2.2. Clinical Laboratory Evaluations

In Part A, blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be analyzed at a central laboratory. PD and ADA will be analyzed at a specialty laboratory as indicated in the General Schedule of Assessments for Part A (Table 1) and Appendix 3. Patients need to be fasting for at least 8 hours prior to the sampling for clinical laboratory tests as from SEB up to EoA.

In Part B, blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be analyzed at local laboratories and results will not be recorded in the eCRF. Blood samples for ADA will be analyzed at a specialty laboratory as indicated in the General Schedule of Assessments for Part B (Table 2) and Appendix 3.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

For all patients of childbearing potential, a urine pregnancy test will be conducted and analyzed locally at the site (on the urine samples taken for urinalysis, if applicable) at all visits in Part A (Table 1) and at visit 1 and 4 of each Treatment Period, at ITPE visits, at EoS/ED and at the discretion of the investigator in Part B (Table 2).

The estimated total maximum blood volume needed for a patient during Part A of the trial (when completing the trial up until the last visit) is between 170 mL for a patient who receives 1 Treatment Period only and 362 mL for a patient who receives a maximum of 6 Treatment Periods. The estimated total maximum blood volume needed for a patient during Part B of the trial (when completing the trial up until the last visit) is between 24 mL for a patient who receives 1 Treatment Period only and 100 mL for a patient who receives 6 Treatment Periods.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial. The investigator will evaluate any change in laboratory values. If the investigator determines a laboratory abnormality to be clinically significant, it will be considered as a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly without being reported as an AE.

The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual. The actual sample collection date and time must be entered in the patient's source documents and on the central lab assessment eCRF page.

Refer to Appendix 4 for the addresses of the laboratories used for sample analyses and storage.

7.2.3. Vital Signs, Physical Examination, and ECG

Assessment of vital signs (supine blood pressure, heart rate, and body temperature), physical examination and ECG will be performed at the time points indicated in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2) (predose at dosing days).

Supine blood pressure and heart rate will be measured using standard equipment after 10 minutes rest on a bed.

It is recommended that the method used to measure body temperature at SEB is maintained throughout the trial for each patient.

A physical examination will include at a minimum an assessment of general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological system.

Weight will be measured at SEB, at the EoA/ED visit, at visit 1 of Part B, at the EoS/ED visit, and can be repeated at any visit when there is an obvious weight change compared to the last weight assessment. Patients will be required to remove their shoes and wear light indoor clothing for this measurement.

A 12-lead ECG will be recorded locally as per local regulations in the supine position after the patient has rested in this position for at least 10 minutes. The assessments on heart rate, PR, QT and QRS intervals will be read centrally.

7.2.4. Suicidality Assessment

As is recommended for trials involving a biological product for a neurological indication, a prospective assessment for suicidal ideation and behavior will be included in this clinical trial (Part A only).

This so-called suicidality assessment will be conducted by specifically asking the following question, derived from the PHQ-9:

- "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?"

The patient will be asked this question at each visit and the response documented. Response options as per the PHQ-9 are limited to the following: *"not at all," "several days," "more than half the days"* or *"nearly every day."*

This specific question was selected for the reported significant linear relationship between the item 9 score of the PHQ-9 and the risk of subsequent suicide attempt.[17]

7.2.5. Medical and Surgical History

Clinically significant findings and pre-existing conditions present in a patient prior to SEB must be reported on the relevant medical history/current medical conditions page of the eCRF.

Information should be provided on medical and surgical history, and concomitant medical conditions specifying those ongoing at SEB.

7.2.6. Data Safety Monitoring Board (DSMB)

The sponsor will appoint a DSMB consisting of an independent group of clinical experts, who are not participating in the trial. They will be supplemented by an independent statistician. The objective of the DSMB will be to review all safety data (including the overall number of patients treated up to that point, rates, and patient-level details). Fixed meetings will be scheduled based on the recruitment rate into the trial, and incidence of (S)AEs. In addition, ad hoc meetings can be requested at any time during the trial by either the sponsor or the DMSB. The DSMB will advise the sponsor concerning continuation, modification or termination of the trial after every meeting.

The composition, objectives, and role and responsibilities of the independent DSMB will be described in a DSMB charter, agreed with the DSMB members and sponsor. The DSMB charter will also define and document the content of the safety summaries, and general procedures (including communications).

7.2.7. Visit Reminder/Subject ID Card

Patients must be provided with the address and telephone number of the main contact for information about the clinical trial. The investigator must therefore provide a “Visit Reminder/Subject ID Card” to each patient. In an emergency situation this card serves to inform the responsible attending physician that the patient is in a clinical trial and that relevant information may be obtained by contacting the investigator. Patients must be instructed to keep the card in their possession at all times.

7.3. Pharmacodynamics

In Part A, the PD markers (total IgG and IgG subtypes [IgG1, IgG2, IgG3 and IgG4], and autoantibodies [anti-AChR antibodies for the AChR-Ab seropositive patients and anti-MuSK antibodies for the MuSK-Ab seropositive patients]) will be measured at the time points as indicated in Table 1. Information on the AChR/MuSK-Ab serotype is available from trial ARGX-113-1704.

These PD markers will be determined using validated assays. The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF.

7.4. Anti-Drug Antibodies

Blood samples to assess ADA will be collected predose at the time points as indicated in Table 1 and Table 2. At baseline (SEB, TP_nB, and TPE_nB), confirmatory and titer analysis will be performed using a validated ADA assay. Samples having a positive ADA titer will be further investigated in a neutralizing ADA assay. The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF.

8. STATISTICS

The statistical analyses will be performed by sponsor's designated CRO using statistical analysis systems SAS® (SAS Institute, Cary, NC, United States [US]) version 9.2 or higher, and the software package R, if applicable. The standard operating procedures (SOPs) and work instructions of sponsor's designated CRO will be used as the default methodology if not otherwise specified.

Any change to the data analysis methods described underneath will be mentioned in the statistical analysis plan (SAP). Any additional analysis, and the justification for making the change, will be described in the Clinical Trial Report (CTR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Due to the single-arm, open-label nature of the design, evaluation of all endpoints will be essentially descriptive. Endpoints will be summarized by treatment (as received in ARGX-113-1704).

8.1. Determination of Sample Size

Not applicable.

8.2. Analysis Populations

The analysis population will consist of all patients who rolled over from trial ARGX-113-1704.

8.3. Patient Disposition, Characteristics and Concomitant Medication

A tabular presentation of the patient disposition will be provided. It will include the number of patients enrolled, completed (by cycle), as well as the number of early discontinuations (including rescued patients), with reasons for discontinuation from trial treatment or trial and major protocol deviations.

A listing will be presented to describe dates of SEB, completion or early discontinuation and the reason for early discontinuation, if applicable, for each patient.

Patient characteristics will be recorded prior to enrollment and will be listed and summarized. Overall summaries will include descriptive statistics for continuous measures (number of observations, mean, standard deviation, median, minimum and maximum) and for categorical measures (sample size, frequency, and percent). Patient characteristics include but are not limited to age, sex, race, weight, and body mass index (BMI).

Use of concomitant medication will be summarized with frequency and percentage. All concomitant medications used will be listed.

8.4. Statistical Methods

8.4.1. Primary and Secondary Endpoint Analyses

All endpoints will be summarized in all enrolled patients and by means of descriptive statistics.

Frequency tables will be made for all binary variables, ie, AEs, by cycle and overall.

Summary statistics will be provided for the continuous endpoints (eg, laboratory values, vital signs, ECGs) in terms of absolute values and changes from TP_1B by cycle and available time points.

8.4.2. Tertiary Endpoint Analyses

The tertiary endpoints will be summarized descriptively.

Summary statistics will be provided for the continuous endpoints (eg, total MD-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies) in terms of absolute values, changes from TP_1B or changes from TP_nB, by cycle and available time points. For levels of total IgG and subtypes and also anti-AChR/anti-MuSK antibodies, the percentage change from TP_1B and from TP_nB will also be presented.

Frequency tables will be made for incidence and prevalence of ADA to efgartigimod.

8.5. Interim Analyses

Interim analyses might be performed to support questions for authorities and/or submissions.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by the Ethics Committee), ICH GCP, and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the trial at the trial site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other trial documents, refers to the investigator or authorized trial personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized trial personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

9.2. Quality Control of Data

Quality control will be applied to each stage of data handling.

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

- Investigator meetings
- Central laboratories for clinical laboratory parameters and ECGs
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Ongoing oversight by Clinical Trial Monitors of safety parameters and adherence to selection criteria
- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the CTR
- To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety and disease severity evaluations.

In addition, sponsor and/or sponsor's designated CRO Clinical Quality Assurance (CQA) Department may conduct periodic audits of the trial processes, including, but not limited to trial site, or site visits, central laboratories, vendors, clinical database, and final CTR. When audits are conducted, access must be authorized for all trial-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

9.3. Monitoring

The sponsor has engaged the services of a CRO to perform all clinical trial monitoring functions within this clinical trial. Sponsor's designated CRO monitors will work in accordance with SOPs of the CRO.

Monitoring visits must be conducted according to the applicable ICH GCP guidelines to verify that, among others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of patients are being protected.
- Trial is conducted in accordance with the currently approved protocol, any other trial agreements and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the Clinical Trial Monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

The Clinical Trial Monitor will perform an eCRF review and Source Document Verification (SDV).

The Source Documentation Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the Clinical Trial Monitor and investigator and should be filed in the investigator's trial file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the Source Documentation Agreement Form.

Upon completion or premature discontinuation from the trial, the Clinical Trial Monitor will conduct site closure activities with the investigator and site staff as appropriate, in accordance with applicable regulations, ICH GCP guidelines and CRO/sponsor procedures.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

9.4. Data Management

Data generated within this clinical trial will be handled according to the SOPs of the Data Management and Biostatistics departments of the sponsor's designated CRO.

Case report forms are provided for each patient in electronic format. It will be transcribed by the trial site staff from the source documents onto the eCRF. Date must be entered in English and guidelines for eCRF completion, including the collection of investigator's e-signature, will be provided by the CRO. Appropriate training and security measures will be completed with the investigator and all authorized trial site staff prior to the trial being initiated and any data being entered into the system for any trial patient at the site.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They can include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc. The eCRFs should be completed by the investigator or a qualified designee from the site as soon as the data are available.

As a matter of regulation, the investigator is responsible for the accuracy and authenticity of all clinical data entered onto eCRFs. Prior to database lock, each completed eCRF must be reviewed for accuracy by the investigator, corrected as necessary and then approved. The investigator's e-signature serves to attest that the information contained on the eCRFs has been reviewed by the investigator and is true and accurate. The investigator will be required to electronically sign off the eCRF.

The data will be verified for missing data, inconsistencies, and for necessary medical clarifications. Queries arising from these checks will be flagged to the trial site, and the trial site staff will correct data, confirm or clarify data as appropriate. The CRO will provide the details of the review process in a data management plan and monitoring plan. Any change, including the issuing of queries, will be fully audit trailed by the EDC application, meaning the name of the person, time, and date stamp are recorded, as well as the reason for change.

Data will also be provided by third party vendors, such as the results generated by the central labs, the Interactive Response Technology (IRT) provider, or centralized ECG reading. These data will need to be reconciled with the data recorded in the eCRF before it can be merged with the eCRF data into the clinical database. The CRO will provide a data management plan detailing this reconciliation.

Adverse events, concomitant diseases/medical history terms will be assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term, and primary system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

Prior and concomitant medications will be classified according to active drug substance using the World Health Organization Drug Dictionary (WHO-DD). The generic name, the preferred name, and the WHO name will be assigned using WHO-DD thesaurus.

The Anatomical Therapeutic Chemical (ATC) classes will be assigned to the prior and concomitant medications.

9.5. Quality Assurance Audit

Trial sites, the trial database and trial documentation may be subject to Quality Assurance audit during the course of the trial by the sponsor or sponsor's designee (CRO or other vendor) on behalf of sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

10. ETHICS

10.1. Institutional Review Board or Independent Ethics Committee

The investigator will provide the sponsor or designee with documentation of IRB/IEC approval of the protocol and informed consent documents before the trial may begin at the trial sites. The investigator will supply documentation to the sponsor or designee of the required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the trial. Similarly, the investigator will submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the trial, the investigator will provide the IRB/IEC with a brief report of the outcome of the trial, if required.

10.2. Ethical Conduct of the Trial

This trial will be conducted, and the informed consent will be obtained, according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

To comply with the Declaration of Helsinki (2013), argenx is assessing the appropriateness and possibility of making the study drug available for clinical study participants post-trial.

10.3. Patient Information and Informed Consent

The ICF, will be used to explain the risks and benefits of trial participation to the patient in simple terms before the patient rolled over into the trial. A separate ICF will be given in case of pregnancy of a female partner of male patient. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the trial, and that the patient is free to withdraw from the trial at any time. Written consent must be given by the patient and/or legally acceptable representative, after the receipt of detailed information on the trial.

All ICFs must be available in the local and vernacular languages required at the site and include patient information sheets/brochures that outline the trial procedures. All ICF(s) must be signed and dated by the patient or a legally acceptable representative.

For patients who are unable to read and write, the patient information sheet and ICF(s) should be read to the patient in his/her native language in the presence of a legally acceptable representative who is literate and not affiliated with the trial. The patient having understood the information given to him/her in the presence of a legally acceptable representative will thumbprint the ICF(s) and the same will be countersigned by the legally acceptable representative. If the patient or legally acceptable representative cannot read, then an impartial witness will witness and attest the entire consent process and will be required to sign the ICF.

Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including SEB tests and assessments.

The investigator is responsible for ensuring that informed consent is obtained from each patient or legally acceptable representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of efgartigimod. The investigator will provide each patient with a copy of the signed and dated ICF(s).

10.4. Patient Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

11. TRIAL ADMINISTRATION

11.1. Data Handling and Record Keeping

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

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

No records should be disposed of without the written approval of argenx BVBA.

For trials conducted outside the US under a US investigational new drug (IND), the principal investigator must comply with US FDA IND regulations and with those of the relevant national and local health authorities.

11.2. Direct Access to Source Data/Documents

The sponsor or designee and auditor may access patient records for the purpose of monitoring this trial, auditing, and managing progress details. The investigator must be fully aware that the sponsor or designee and auditor can inspect or verify documents to verify patient chart and eCRF records. Such information must be kept confidential and must have locked facilities that allow for this. The investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient enrolled into the trial.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the Clinical Trial Monitor at each monitoring visit. The investigator must submit a completed eCRF for each patient who receives efgartigimod, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the trial and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

11.3. Investigator Information

11.3.1. Investigator Obligations

The investigator is responsible for ensuring that all trial site personnel, including sub-investigators, adhere to all applicable regulations and guidelines, including local laws and regulations, regarding the trial, both during and after trial completion. The investigator is responsible for informing the IRB/IEC of the progress of the trial and for obtaining annual IRB/IEC renewal. The investigator is responsible for informing the IRB/IEC of completion of the trial and will provide the IRB/IEC with a summary of the results of the trial.

11.3.2. Protocol Signatures

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the sponsor or representative. By signing the protocol, the investigator confirms in writing that he/she has read, understands, and will strictly adhere to the trial protocol and will conduct the trial in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The trial will not be able to start at any site where the investigator has not signed the protocol.

11.3.3. Publication Policy

All information regarding efgartigimod supplied by the sponsor to the investigator and all data generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The results of the trial will be reported in a CTR.

The CTR written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the trial must be prepared in conjunction with the sponsor and must be submitted to the sponsor for review and comment prior to submission for publication or presentation. Trial patient identifiers will not be used in publication of results.

Authorship will be granted based on scientific input, recruitment efforts, and will be granted upon decision of a publication committee. This committee will include among others the coordinating investigator and the sponsor.

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

11.3.4. Financing and Insurance

The sponsor will fund the trial as outlined in the Clinical Trial Agreement.

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

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

12. REFERENCES

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13. APPENDICES

APPENDIX 1: Myasthenia Gravis Activities of Daily Living

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total score _____	

Source: website MGFA, MG-ADL[19,20]

APPENDIX 2: Quantitative Myasthenia Gravis Score

Quantitative MG score

Test item	None	Mild	Moderate	Severe	Score
Grade	0	1	2	3	
Double vision on lateral gaze right or left (circle one), seconds	61	11–60	1–10	Spontaneous	____
Ptosis (upward gaze), seconds	61	11–60	1–10	Spontaneous	____
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, witho resistance	icomplete	____
Swallowing 4 oz. water (1/2 cup)	Normal	Minimal coughing or throat clearing	Sev coughing /choki or nasal gurg ion	annot allow not attempted)	____
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	ysarti t 10–29	Dysarthria at 9	____
Right arm outstretched (90 degree sitting), seconds	240	9	10–89	0–9	____
Left arm outstretched (90 degree sitting), seconds	240	90- 39	10–89	0–9	____
Vital capacity, % predicted	≥80	65–	50–64	<50	____
Right-hand grip, kgW					
Men	≥45	15–	5–14	0–4	____
Women		10–29	5–9	0–4	____
Left-hand grip, kgW					
Men	≥3	15–34	5–14	0–4	____
Women		10–24	5–9	0–4	____
Head lifted (45 degree supine),	20	30–119	1–29	0	____
Right leg outstretched (45 degree supine), seconds	00	31–99	1–30	0	____
Left leg outstretched (45 degree supine), seconds	100	31–99	1–30	0	____
			Total QMG score (range, 0–39)		

Source: website MGFA, Quantitative MG score[21,22]

APPENDIX 3: Laboratory Evaluations

Hematology	Hemoglobin, platelet count, white blood cell (WBC) count with WBC differential
Clinical Chemistry	Creatinine, creatinine clearance, blood urea nitrogen (BUN), glucose, glycosylated hemoglobin [HbA1c], alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, albumin, potassium, sodium, calcium, lipid panel (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL], and triglycerides), international normalized ratio (INR) and activated partial thromboplastin time (aPTT)
Urinalysis	Color, clarity/appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination including red blood cell (RBC) count, WBC, cast crystals, bacteria.
Other	Urine human chorionic gonadotrophin (ß-HCG)
Pharmacodynamic (PD) markers	Total IgG and subtypes (IgG1, IgG2, IgG3, and IgG4), and AChR-Ab (binding) levels in AChR-Ab seropositive patients only and anti-muscle-specific kinase (MuSK) antibodies in MuSK-Ab seropositive patients only. Information on the AChR/MuSK-Ab serotype (seronegative or seropositive) is available from trial ARGX-113-1704.
Anti-drug antibodies (ADA)	Levels of anti-efgartigimod binding and neutralizing antibodies (if applicable)

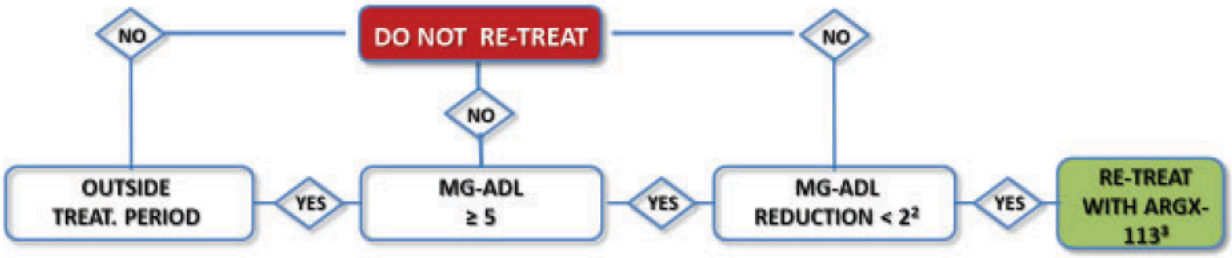
Note: For Part A, all blood and urine samples will be collected locally (predose on dosing days) and analyzed at a central or specialty laboratory. For Part B, blood and urine samples for clinical chemistry, hematology, and urinalysis will be analyzed locally, while ADA samples will be analyzed at a specialty laboratory.

APPENDIX 4: Administrative Structure

Clinical Laboratories (Part A only)	
United States	Covance 8211 SciCor Drive Indianapolis, IN 46214 United States
Europe	Covance Rue Moise-Marcinhes 7 CH – 1217 Meyrin Geneva Switzerland
Japan	Covance Japan Co., Ltd. Harumi Triton Square Office Tower Y 8F,1-8-11, Harumi, Chuo-ku, Tokyo 104-6108 Japan

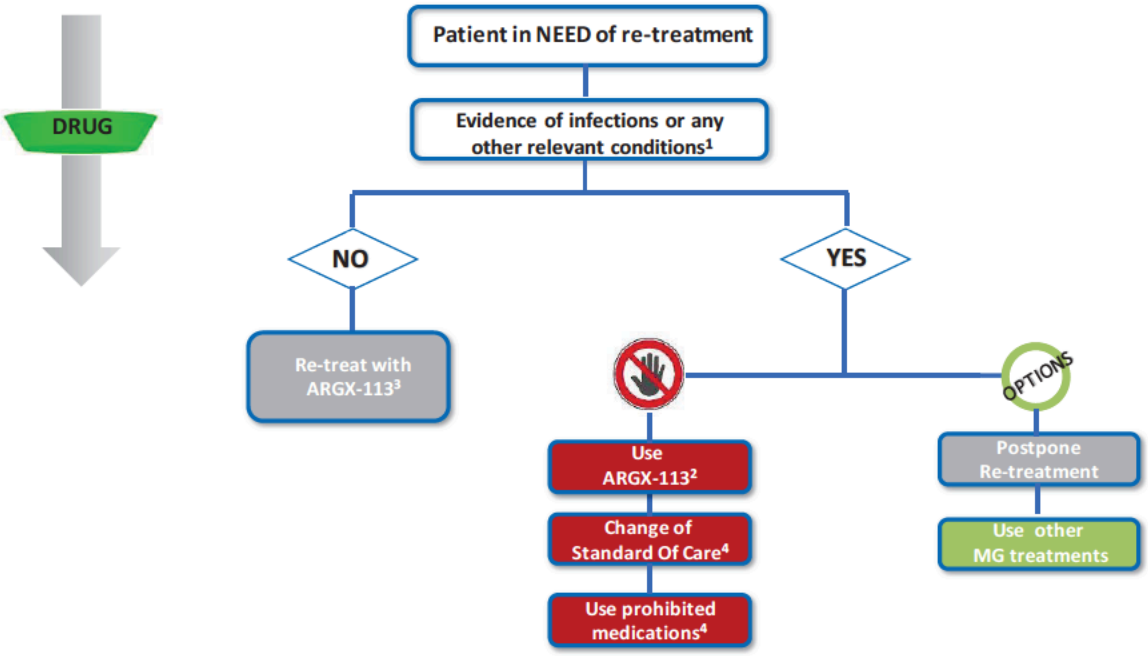
Analysis of Pharmacodynamics (PD), Anti-Drug Antibodies (ADA)	
France	SGS France 90 Avenue des Hauts de la Chaume BP. 28 86281 Saint-Benoît Cedex France
Long-Term Storage of Pharmacodynamics (PD), Anti-Drug Antibodies (ADA)	
Germany	Brooks Life Science, BioStorage Technologies GmbH Im Leuschnerpark 1b 64347 Griesheim Germany
Study Monitoring/Medical Monitoring	
United States	Syneos Health™ group company including INC Research, LLC, together with INC Research UK Limited 3201 Beechleaf Court, Suite 600 Raleigh, North Carolina 27604-1547 United States Phone +1 919-876-9300
Germany	EastHORN Clinical Service GmbH Im Mediapark 6c 50670 Cologne Germany
Clinical Trial Supply Management	
Belgium	CSM Watson & Crick Hill Rue Granbonpré 11 B-1435 Mont-Saint-Guibert Belgium
Data Management and Biostatistics	
Belgium	SGS Life Sciences (SGS LS), a division of SGS Belgium NV Generaal de Wittelaan 19A b5 BE – 2800 – Mechelen Belgium
Drug-Safety Reporting	
United States	Parexel International 8 Federal Street Billerica MA 01821 United States

APPENDIX 5: Decision Tree for Re-Treatment in Part A (Part 1)



[1]*First time-point at which these conditions occur*
[2]*MG-ADL decrease of <2 compared to corresponding treatment period baseline*
[3]*if no infection or confounding conditions*

APPENDIX 6: Decision Tree for Re-Treatment in Part A and Part B (Part 2)



[1]*Conditions that may interfere with the correct interpretation of the data or put the patient at an undue risk*
[2]*Re-treatment with ARGX-113 may be re-considered at the time of the next re-treatment cycle*
[3] *In case of a change (dose decrease) of SoC occurred, the specific SoC stability criteria has to be met before retreating with ARGX-113 (Part A only)*
[4]*Only for Part A. In Part B a change in SoC is allowed and there are no prohibited medications.*

APPENDIX 7: Summary of Changes From Prior Amendments

Protocol Version 3.1 compared to Protocol Version 3.2

Changes from Protocol Version 3.1 compared to Protocol Version 3.2 are summarized below.

Of note: updates of headers/footers and tables of contents as well as editorial changes regarding layout, font, and format are not recorded in this summary.

Section	Change	Rationale
Table 2 General Schedule of Assessments for Part B	Assessments highlighted in yellow indicate assessments … changed to Assessments highlighted by use of bold italics indicate assessments …	Correction
Appendix 8 Guidance to Sites in Case of Suspected COVID-19 in Patients	1. Does the patient have symptoms such as cough, fever, muscle pain, shortness of breath? - If NO: Go to Questions 2 and 3. - If YES: • If the patient is not tested for COVID-19: The visit will take place after at least 14 days post first symptoms and only if the patient is symptom free… … • If the patient is tested and found to be COVID-19 positive: The patient can only come to the site once he/she is symptom free, and so … changed to 1. Does the patient have symptoms, such as cough, fever, muscle pain, shortness of breath*? - If NO: Go to Questions 2 and 3. - If YES: • The patient should be tested for COVID-19: The Investigator needs to document a positive COVID-19 test as an AESI. The anonymized result needs to be sent to the sponsor for filing. If COVID-19 safety measures are stopped according to local regulations, COVID-19 tests should continue to be performed and the results sent to the sponsor. *Shortness of breath includes an otherwise unexplained deterioration in the patient's MG-ADL score for breathing. In cases where the MG-ADL score for breathing is 2 or 3 additional COVID-19 testing should	Changes have been made to allow for COVID-19 testing of patients exhibiting symptoms of the disease.

Section	Change	Rationale
	be carried out. The exception to this is when a patient has an MG-ADL score for breathing of 2 at baseline. In such cases the patient should only be tested when the MG-ADL score for breathing returns to 2 after previous improvement or when it deteriorates to 3. The visit will only take place once the patient has a negative test for COVID-19… … • If the patient is tested and found to be COVID-19 positive: The patient can only come to the site once he/she has a negative test for COVID-19, and so …	

As the COVID-19 pandemic poses issues for both sites and patients and presents unprecedented challenges in uncharted territory, this crisis prompted the sponsor to perform a critical review of both efgartigimod administration and changes needed to the study in order to safeguard patient safety, while still being able to gather additional data.

Therefore, for the global amendment of the ARGX-113-1705 protocol from version 3.0 to 3.1 an addendum has been added to the study detailing the safety measures and changes to be implemented in the current situation. The risk/benefit, safety profile, guidance for site conduct and potential changes in the Schedule of Assessments are detailed in Appendix 8.

This will be a temporary change to the procedures of the study and will only last as long as the COVID-19 pandemic affects the ability of the patients to attend their study visits.

Protocol Version 3.0 compared to Protocol Version 3.1

Changes from Protocol Version 3.0 compared to Protocol Version 3.1 are summarized below.

Of note: updates of headers/footers and tables of contents as well as editorial changes regarding layout, font, and format are not recorded in this summary.

An additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension to Part A of the trial will be a maximum of 2 years and will also enable additional long-term safety and tolerability data to be collected.

The extension part (Part B) will include fewer assessments to minimize the burden for the patients and changes in the SoC are allowed.

Long-term safety follow-up will be carried out via local lab testing at the discretion of the investigator, as well as follow-up of AEs.

In Part A of the trial MG-ADL guidelines need to be followed for re-treatment. In Part B, MG-ADL will serve as a guide for re-treatment, but it is up to the investigator to decide when the patient will be re-treated.

Protocol Version 2.0 compared to Protocol Version 3.0

Changes from Protocol Version 2.0 compared to Protocol Version 3.0 are summarized below.

Of note: updates of headers/footers and tables of contents as well as editorial changes regarding layout, font, and format are not recorded in this summary.

Where changes have been made in a few words only these have been highlighted using *italics*.

Section	Change	Rationale
SUMMARY OF CHANGES	A summary and table highlighting the differences between Part A and Part B of the trial was added. The Summary of Changes tables have been moved to Appendix 7.	Due to the number of changes, and therefore the size of the tables required to describe all the changes made to the protocol, the detailed Summary of Changes tables have been moved to Appendix 7.
SYNOPSIS Trial Duration:	The trial duration will be 1 year. changed to The trial duration will be up to maximum 3 years. The trial consists of two parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first).	See summary above.
SYNOPSIS Objectives: 2. TRIAL OBJECTIVES 2.3. Tertiary Objectives	Tertiary Objectives: … • To evaluate the immunogenicity of ARGX-113. changed to Tertiary Objectives: Part A only: … Part A and B: • To evaluate the immunogenicity of ARGX-113.	
SYNOPSIS Methodology: DESCRIPTION	This is a 1-year, single-arm, open-label, multicenter, Phase 3 follow-on extension trial of ARGX-113-1704 to evaluate the long-term safety and tolerability of ARGX-113 in patients with gMG.	

Section	Change	Rationale
4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology DESCRIPTION	A variable number of Treatment Periods consisting of 4 weekly infusions of ARGX-113 (10 mg/kg of body weight) infused over a period of 3 weeks will be administered to eligible patients on an "as needed basis" on top of their standard of care (SoC) in Treatment Periods. … The Study Entry Baseline (SEB) will be set at the first trial visit, while the Baseline of each subsequent Treatment Period (TP_nB) will be set at Visit 1 of each corresponding Treatment Period. changed to This is a 3-year (maximum), single-arm, open-label, multicenter, Phase 3 follow-on extension trial of ARGX-113-1704 to evaluate the long-term safety and tolerability of ARGX-113 in patients with gMG. The trial consists of two parts: Part A (1 year) and Part B (maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). The additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension will also enable additional long-term safety and tolerability data to be collected. A variable number of Treatment Periods consisting of 4 weekly infusions of ARGX-113 (10 mg/kg of body weight) infused over a period of 3 weeks will be administered to eligible patients on an "as needed basis" on top of their standard of care (SoC). … The Study Entry Baseline (SEB) will be set at the first trial visit, while the Baseline of each subsequent Treatment Period (TP_nB for Part A or TPE_nB for Part B) will be set at Visit 1 of each corresponding Treatment Period.	
SYNOPSIS Methodology: (RE-)TREATMENT	(RE-)TREATMENT changed to (RE-)TREATMENT (Part A)	

Section	Change	Rationale
4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology (RE-)TREATMENT		
SYNOPSIS Methodology: (RE-)TREATMENT (Part A) 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology (RE-)TREATMENT (Part A)	Patients who show a treatment failure to ARGX-113 for three consecutive Treatment Periods will be discontinued from further treatments with ARGX-113 but will remain in the trial to receive appropriate alternative MG therapy. Treatment failure means the absence of a decrease of at least 2 points in total MG-ADL score compared to the corresponding TP_nB in at least 50% of the assessments (i.e., TP_nV2, TP_nV3, TP_nV4 and the first post-Treatment Period visit). If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score but cannot complete the entire Treatment Period within the duration of the trial the patient should receive appropriate alternative MG therapy and continue to the EoS visit. changed to Patients who show a treatment failure to ARGX-113 for three consecutive Treatment Periods will be discontinued from the trial. Treatment failure means the absence of a decrease of at least 2 points in total MG-ADL score compared to the corresponding TP_nB in at least 50% of the assessments (i.e., TP_nV2, TP_nV3, TP_nV4 and the first post-Treatment Period visit). If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score but cannot complete the entire Treatment Period within the duration of Part A (re-treatment in Part A can start at the latest on Day 336) then the patient will be transitioned to Part B after completing the End of Part A (EoA) visit. If the patient is not willing or able to continue to Part B then he/she should continue to the EoA visit. The transition to Part B can be either at $ITPE_0V1$ or TPE_1V1, depending on the patient's status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.	

Section	Change	Rationale
	(RE-)TREATMENT (Part B) If the patient feels that his/her condition has deteriorated, the Investigator may decide to start a new Treatment Period at the time of an Intertreatment Period (ITPE) visit or the patient may contact the Investigator for an unscheduled visit. Each patient can start a (new) Treatment Period with ARGX-113 when all the following criteria apply: The patient has completed the previous Treatment Period (i.e., after Visit 4)*; AND The Investigator determines that the patient will benefit from re-treatment; AND There is at least 1 calendar month (minimum 4 weeks) between Treatment Periods (i.e., between TPE_nV4 and $TPE_{n+1}V1$). *A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions in Section 4.4.3 are met. However, patients may not receive (re-)treatment with ARGX-113 if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. If a patient becomes eligible for (re-)treatment with ARGX-113 but cannot complete the entire Treatment Period within the duration of the trial, the patient should continue to the EoS visit. If the Investigator considers that the patient will not have a clinical benefit from (re-)treatment then the patient cannot start a new Treatment Period. The patient should then continue to the EoS visit.	
SYNOPSIS Methodology: STANDARD OF CARE (SoC) 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design	Permitted SoC for MG treatment under this protocol include … changed to In Part A: Permitted SoC for MG treatment under this protocol include … In Part B: A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of	See summary above. Part B allows for freedom of changing therapy and there will be no restrictions on the type of therapy that can be used. This because Part B will shift to a more real-life approach.

Section	Change	Rationale
Methodology STANDARD OF CARE	the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice. Plasma exchange (PLEX), intravenous immunoglobulin (IVIg), immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.	
SYNOPSIS Methodology: TIME BETWEEN TREATMENT CYCLES 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology TIME BETWEEN TREATMENT CYCLES	TIME BETWEEN TREATMENT CYCLES At the end of each Treatment Period, … The visit frequency in the Intertreatment Period is every 30 days (± 2 days) after the previous visit. changed to TIME BETWEEN TREATMENT PERIODS At the end of each Treatment Period, … For Part A, the visit frequency in the Intertreatment Period is every 30 days (± 2 days) after the previous visit. For Part B, the visit frequency in the Intertreatment Period is every 90 days (± 7 days) after the previous visit. If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then the EoA visit should be performed instead.	Changed to be consistent with ARGX-113-1704. A Treatment Cycle is a Treatment Period + follow-up. This section is describing Treatment Periods. Since in Part B the dosing regimen and visit schedule are more in line with a real-life situation with quarterly visits to the treating physician, the frequency of the ITP visits has been reduced to once every 90 days. However, should the Investigator, together with the patient, deem it necessary the patient can return sooner.
SYNOPSIS Methodology: RESCUE THERAPY 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology RESCUE THERAPY 6. TRIAL TREATMENT	RESCUE THERAPY Rescue therapy will be limited to *plasma exchange (PLEX), intravenous immunoglobulin (IVIg),* immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination. … In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from *trial treatment*. changed to RESCUE THERAPY (Part A only) Rescue therapy will be limited to *PLEX, IVIg,* immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination.	See summary above.

Section	Change	Rationale
6.8. Prior Treatments and Concomitant Medications 6.8.2. Rescue Therapy	… In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from *the trial*.	
SYNOPSIS Methodology: EARLY DISCONTINUATION FROM THE TRIAL 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology EARLY DISCONTINUATION FROM THE TRIAL	Section deleted: EARLY DISCONTINUATION FROM THE TRIAL Any patient prematurely discontinuing the trial should perform the EoS/ED assessments.	In order to reduce the burden on the patients, the safety follow-up period has been replaced by 1 safety follow-up visit. As a result there is no longer a difference between discontinuation from trial treatment or from the trial. Therefore if the patient can no longer receive the study drug for any reason, the patient will be able to leave the trial after a limited safety follow-up period. If warranted further safety follow-up can be performed by the Investigator and the relevant information captured in the safety database.
SYNOPSIS Methodology: EARLY DISCONTINUATION FROM TRIAL TREATMENT 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology EARLY DISCONTINUATION FROM TRIAL TREATMENT	EARLY DISCONTINUATION FROM TRIAL TREATMENT Patients who discontinue early from trial treatment within a Treatment Period will have to complete the End of Treatment (EoT) assessments and complete the remaining visits in the current Treatment Period according to the General Schedule of Assessments (Table 1). These patients will not receive any further administration of ARGX-113 during the trial and will continue to be followed for safety and disease severity as per Schedule of Assessments for Patients who Discontinue Early from Trial Treatment (Table 2). Patients who discontinue early from trial treatment in the Intertreatment Period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per Table 2. changed to EARLY DISCONTINUATION For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4, Figure 1, and Figure 2).	

Section	Change	Rationale
	Patients who discontinue early from the trial within a Treatment Period should perform the planned assessments of the corresponding Treatment Period visit. These patients will not receive any further administration of ARGX-113 during the trial and will return for the ED visit one month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the Investigator. Patients who discontinue early from the trial between the last visit of a Treatment Period (TP_nV4 or TPE_nV4) and the next Intertreatment Period visit (ITP_nVn or $ITPE_nVn$) should perform the ED assessments one month (30 ± 2 days) after the last dose administration. Patients who discontinue early from the trial at the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments, instead of the ITP_nVn (Part A) or $ITPE_nVn$ (Part B) assessments. Patients who discontinue early from the trial after the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments. Any patient prematurely discontinuing the trial during Part A should perform the EoA/ED assessments according to the General Schedule of Assessments for Part A (Table 1). Any patient prematurely discontinuing the trial during Part B should perform the EoS/ED assessments according to the General Schedule of Assessments for Part B (Table 2).	
SYNOPSIS TEMPORARY INTERRUPTION FROM TRIAL TREATMENT 4. INVESTIGATIONAL PLAN 4.1. Summary of Trial Design Methodology TEMPORARY INTERRUPTION FROM TRIAL TREATMENT	A patient who does not need to be discontinued early from *trial treatment* might still … A schematic of trial design is presented in Figure 1. changed to: A patient who does not need to be discontinued early from *the trial* might still … Patients for whom treatment is interrupted will have to complete the current Treatment Period and will continue the trial as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2) but without drug administration. A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions mentioned above are met. A schematic of the trial design is presented in Figure 1 for Part A and in Figure 2 for Part B.	

Section	Change	Rationale
SYNOPSIS Exclusion Criteria 4. INVESTIGATIONAL PLAN 4.3. Selection of Trial Population 4.3.2. Exclusion Criteria	1. Patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from randomized treatment for rescue or pregnancy reasons or an *(S)AE that might jeopardize the safety of the patient in that trial*. changed to 1. Patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from randomized treatment for rescue or pregnancy reasons or an *SAE that is likely to result in a life-threatening situation or pose a serious safety risk*.	Corrected. This was amended in Section 4.4.2 in a previous amendment (2.0), but was not amended in the exclusion criteria.
SYNOPSIS Criteria for Evaluation: 3. TRIAL ENDPOINTS 3.1. Primary Endpoint 3.2. Secondary Endpoint 3.3. Tertiary Endpoints	<u>Primary Endpoint</u>: • Incidence and severity of AEs, SAEs, vital signs, electrocardiogram (ECG) and laboratory assessments over 1 year in AChR-Ab seropositive patients. <u>Secondary Endpoints:</u> • Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments over 1 year in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients). • Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments at each Treatment Period in AChR-Ab seropositive patients. • Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments at each Treatment Period in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients). <u>Tertiary Endpoints</u> • To evaluate the disease severity as assessed by total MG-ADL score changes compared to SEB and the corresponding TP_nB in AChR-Ab seropositive patients. • To evaluate the disease severity as assessed by total MG-ADL score changes compared to SEB and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients). • To evaluate the disease severity as assessed by total QMG score changes compared to SEB and the corresponding TPnB in AChR-Ab seropositive patients. • To evaluate the disease severity as assessed by total QMG score changes compared to SEB and the	Endpoints streamlined to reflect what will actually be summarized and labels added to clarify what will be analyzed in Part A and Part B of the trial. Corrected to reflect that changes from the treatment period baseline of the first cycle will be summarized (instead of changes from SEB) as patients might start the study with an intertreatment period. "To evaluate the disease severity as assessed by" should not be part of an endpoint definition. For Part B only immunogenicity will be characterized as a tertiary endpoint. Furthermore, only safety and tolerability will be followed up and no PD markers will be summarized.

Section	Change	Rationale
	corresponding TPnB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients). • Percentage decrease (compared to SEB and the corresponding TPnB) of total IgG level and IgG subtypes in ARGX-113 (re-)treated patients. • Percentage decrease (compared to SEB and the corresponding TPnB) of autoantibodies (anti-AChR antibodies and anti-MuSK antibodies) in ARGX-113 (re-)treated patients. • Incidence of anti-drug antibodies (ADA) to ARGX-113 at SEB and at each Treatment Period. changed to <u>Primary Endpoint</u>: • Incidence and severity of AEs, SAEs, vital signs, electrocardiogram (ECG) and laboratory assessments over the duration of the trial in AChR-Ab seropositive patients. <u>Secondary Endpoint:</u> • Incidence and severity of AEs, SAEs, vital signs, ECG and laboratory assessments over the duration of the trial in the overall population (AChR-Ab seropositive patients and AChR-Ab seronegative patients). <u>Tertiary Endpoints:</u> Part A only: • Total MG-ADL score changes compared to the Treatment Period Baseline of the first cycle (TP_1B) and the corresponding TP_nB in AChR-Ab seropositive patients. • Total MG-ADL score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients). • Total QMG score changes compared to TP_1B and the corresponding TP_nB in AChR-Ab seropositive patients. • Total QMG score changes compared to TP_1B and the corresponding TP_nB in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients). • Percentage decrease (compared to TP_1B and the corresponding TP_nB) of total IgG level and IgG subtypes in ARGX-113 (re-)treated patients. • Percentage decrease (compared to TP_1B and the corresponding TP_nB) of autoantibodies (anti-AChR	

Section	Change	Rationale
	antibodies and anti-MuSK antibodies) in ARGX-113 (re-)treated patients. Part A and B: • Incidence and prevalence of anti-drug antibodies (ADA) to ARGX-113.	
SYNOPSIS Statistical Methods and Plan:	A Statistical Analysis Plan detailing all statistical methods and analyses will be issued before *the* database lock. A summary of the plan is described below. All endpoints will be tested in all enrolled patients and by means of descriptive statistics. All comparisons of endpoints between Treatment Periods will be purely descriptive. Summary statistics will be provided for the continuous endpoints (e.g., total MG-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies, laboratory values, vital signs, ECG) in terms of absolute values and changes from SEB and changes from Treatment Period Baseline (TPB), at each Treatment Period (including Intertreatment Period) and available time points. Frequency tables will be made for all binary variables, i.e., AEs and ADA for all Treatment Periods and overall (including Intertreatment Periods) and available time points. changed to A Statistical Analysis Plan detailing all statistical methods and analyses will be issued before *any* database lock. A summary of the plan is described below. All endpoints will be summarized in all enrolled patients and by means of descriptive statistics. Summary statistics will be provided for the continuous endpoints (e.g., total MG-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies, laboratory values, vital signs, ECG) in terms of absolute values, changes from TP_1B or changes from TP_nB, by cycle and available time points. Frequency tables will be made for all binary variables, i.e., AEs and ADA by cycle and overall.	Corrected to reflect that changes from the treatment period baseline of the first cycle will be summarized (instead of changes from SEB), as patients might start the study with an intertreatment period. AEs and ADA will be summarized by cycle, not by timepoint.

Section	Change	Rationale
Table 1 General Schedule of Assessments	Title: Table 1 General Schedule of Assessments changed to Table 1 General Schedule of Assessments for Part A	See summary above.
Table 1 General Schedule of Assessments End of Study/Early Discontinuation	End of Study/Early Discontinuation EoS/ED changed to End of Part A/Early Discontinuation EoA/ED	
Table 1 General Schedule of Assessments Trial Day (Visit Windows)	Trial Day (Visit Windows): (X+8)±1/ (X+15)±1/ (X+22)±1 changed to (X+7)±1/ (X+14)±1/ (X+21)±1	Trial Day (Visit Windows) timings were corrected.
Table 1 General Schedule of Assessments Trial Day (Visit Windows)	Trial Day (Visit Windows): Y (±2) changed to Y+30 (±2)	Clarification added that these visits occur 30 days after the previous visit.
Table 1 General Schedule of Assessments	Deleted: EoT_n	There is no End of Treatment visit.
Table 1 General Schedule of Assessments	Text added: Y=previous visit	Y added to footnotes for clarification.
Table 1 General Schedule of Assessments Footnote	EoS/ED=End of Study/Early Discontinuation; changed to EoA/ED=End of Part A/Early Discontinuation;	See summary above.
Table 1 General Schedule of Assessments Footnote	Deleted: EoT=End of Treatment	There is no End of Treatment visit.
Table 1 General Schedule of Assessments	[b] The intertreatment period visits (ITP_nVn) occur every 30 days after the previous visit. The visit denominator ('n') will start at 1 at each period. At each ITP_nVn, an	See summary above.

Section	Change	Rationale
Footnote b	evaluation of the need for (re-)treatment should be done prior to decide whether assessments listed for ITP_nVn or TP_nV1 are to be performed. changed to [b] The intertreatment period visits (ITP_nVn) occur every 30 days after the previous visit (Y). The visit denominator ('n') will start at 1 at each period. At each ITP_nVn, an evaluation of the need for (re-)treatment should be done prior to deciding whether the assessments listed for ITP_nVn or TP_nV1 are to be performed. If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then this EoA visit should be performed instead. For patients that discontinue at the ITP visit this will then serve as the EoA/ED visit.	
Table 1 General Schedule of Assessments Footnote c	[c] If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score but cannot complete the entire Treatment Period within the trial duration, the patient should receive appropriate alternative MG therapy and continue to the EoS visit. changed to [c] If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score, but cannot complete the entire Treatment Period within Part A of the trial (re-treatment in Part A can start at the latest on Day 336), then the patient will be transitioned to Part B after completing the EoA visit. If the patient is not willing or able to continue to Part B then they should continue to the EoA visit. The transition to Part B can be either $ITPE_0V1$ or TPE_1V1, depending on the patient status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B. Footnote c was added to the assessment End of Part A.	
Table 1 General Schedule of Assessments Footnote d	[d] An unscheduled (UNS) visit can *be on* request of the patient or the Investigator. changed to [d] An unscheduled (UNS) visit can *occur at the* request of the patient or the Investigator.	Use of language corrected.
Table 1 General Schedule of Assessments	[i] Weight will be measured at SEB, at the *EoS/ED* visit, and when there is an obvious weight change compared to the last weight assessment.	See summary above.

Section	Change	Rationale
Footnote i	changed to [i] Weight will be measured at SEB, at the *EoA/ED* visit, and when there is an obvious weight change compared to the last weight assessment.	
Table 1 General Schedule of Assessments Footnote s	[s] For patients who discontinue early from trial treatment, the assessments will depend on the visit at which it was decided that the patient had to discontinue trial treatment (see Section 5.4). Patients who discontinue early from trial treatment within a Treatment Period will have to complete the EoT assessments and complete the remaining visits in the current Treatment Period according to this Schedule of Assessments. These patients will not receive any further administration of ARGX-113 during the trial and will continue to be followed for safety and disease severity as per Schedule of Assessments for Patients who Discontinued Early from Trial Treatment (Table 2). Patients who discontinue early from trial treatment in the Intertreatment Period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period per Table 2. changed to [s] For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4). Patients who discontinue early from the trial within a Treatment Period should perform the planned assessments of the corresponding Treatment Period visit. These patients will not receive any further administration of ARGX-113 during the trial and will return for the ED visit one month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the Investigator. Patients who discontinue early from the trial between the last visit of a Treatment Period (TP_nV4) and the next intertreatment period visit (ITP_nVn) should perform the ED assessments one month (30 ± 2 days) after the last dose administration. Patients who discontinue early from the trial at the ITP visit should perform the ED assessments, instead of the ITP_nVn assessments. Patients who discontinue early from the trial after the ITP visit should perform the ED assessments. Footnote s was added to the assessment Early Discontinuation.	In order to simplify the safety follow-up the different scenarios have now been linked to the last dose, in order to see what schedule needs to be followed for further safety follow-up. There is no End of Treatment visit.
Table 2: Schedule of Assessments for	Table 2 was deleted.	Patients will not be followed for safety and disease

Section	Change	Rationale
Patients who Discontinued Early from Trial Treatment[a]		severity every 30 days. The new scenario for early discontinuation means that patients should perform the ED visit instead (at least 30 days after the last administration of study drug).
Figure 1: ARGX-113-1705 Trial Design	Scenario for early discontinuation added.	
Figure 1: ARGX-113-1705 Trial Design	Footnotes for ED, EoA, SEB and SoC added	See summary above.
	Title: Figure 1: ARGX-113-1705 Trial Design changed to Figure 1: ARGX-113-1705 Trial Design for Part A	
	EoS changed to EoA	
Table 2 General Schedule of Assessments for Part B	A new table for the Schedule of Assessments for Part B has been added.	
Figure 2: ARGX-113-1705 Trial Design for Part B	A new figure for the Trial Design for Part B has been added.	
LIST OF ABBREVIATIONS	List of abbreviations updated to include cycle, EoA, EoS, ITPEV, TP, TPE, TPE_nB and TPEV, and EoT removed.	
4. INVESTIGATIONAL PLAN 4.2. Discussion of Trial Design	This trial is designed as a 1-year, single-arm, open-label, follow-on extension trial of ARGX-113-1704. With the exception of patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from trial treatment for rescue or pregnancy reasons or an (S)AE that might jeopardize the safety of the patient in that trial, all participants of trial ARGX-113-1704 who reached the EoS visit (Day 182) are allowed to roll over into this trial. The first visit of trial ARGX-113-1705 will coincide with the last visit of trial ARGX-113-1704 for each patient. changed to	

Section	Change	Rationale
	This trial is designed as a 3-year (maximum), single-arm, open-label, follow-on extension trial of ARGX-113-1704. The trial consists of two parts: Part A (1 year) and Part B (up to maximum 2 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first. The additional part (Part B) was added to ARGX-113-1705 in order to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. This extension will also enable additional long-term safety and tolerability data to be collected. With the exception of patients who discontinued early from trial ARGX-113-1704 or patients who discontinued early from trial treatment for rescue or pregnancy reasons or an SAE that is likely to result in a life-threatening situation or pose a serious safety risk, all participants of trial ARGX-113-1704 who reached the EoS visit are allowed to roll over into this trial. The first visit of trial ARGX-113-1705 will coincide with the last visit of trial ARGX-113-1704 for each patient. In the same way, with the exception of patients who discontinued early from Part A of this trial, all participants of Part A who reached the EoA visit can be transitioned to Part B of this trial. The first visit of Part B of this trial will coincide with the last visit of Part A for each patient.	
4. INVESTIGATIONAL PLAN 4.2. Discussion of Trial Design	A change of the type or dose/regimen of SoC … … The chosen primary and secondary endpoints in this trial are to evaluate the long-term safety and tolerability of ARGX-113 over *1 year and at each Treatment Period* in AChR-Ab seropositive patients and in the overall population (AChR-Ab seropositive and seronegative patients). changed to In Part A, a change of the type or dose/regimen of SoC … … In Part B, a change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of	See summary above. Part B allows for freedom of changing therapy and there will be no restrictions on the type of therapy that can be used. This because Part B will shift to a more real-life approach.

Section	Change	Rationale
	the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice. PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B. The chosen primary and secondary endpoints in this trial are to evaluate the long-term safety and tolerability of ARGX-113 over *the duration of the trial, as well as by cycle*, in AChR-Ab seropositive patients and in the overall population (AChR-Ab seropositive and seronegative patients).	
4. INVESTIGATIONAL PLAN 4.4. Early Discontinuation	4.4. Early Discontinuation … 4.4.1. Early Discontinuation from Trial … Patients must be discontinued early from the trial and complete the EoS/ED visit if: • They withdraw their consent. • The Investigator, after discussion with the sponsor's Medical Director, deems it is in the patient's best interest. All patients are free to withdraw consent from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice to further treatment. Prior to actual withdrawal of consent, an effort should be made to perform a final set of assessments as per EoS/ED visit in the General Schedule of Assessments (Table 1). Investigators will make and document all efforts made to contact those patients who do not return for scheduled visits. changed to 4.4. Early Discontinuation … … Patients must be discontinued early from the trial if: • They withdraw their consent. • The Investigator, after discussion with the sponsor's Medical Director, deems it is in the patient's best interest. • Patient is pregnant. • Patients receives rescue therapy.	In order to reduce the burden on the patients, the safety follow-up period has been replaced by 1 safety follow-up visit. As a result there is no longer a difference between discontinuation from trial treatment or from the trial. Therefore if the patient can no longer receive the study drug for any reason, the patient will be able to leave the trial after a limited safety follow-up period. If warranted further safety follow-up can be performed by the Investigator and the relevant information captured in the safety database.

Section	Change	Rationale
	• Patient develops an SAE that is likely to result in a life-threatening situation or pose a serious safety risk to the patient. • Prohibited medication is taken (see Section 6.8.1). Patients might discontinue early from the trial if: • Patient has clinical evidence of bacterial, viral or fungal disease or any other significant disease which could confound the results of the trial or put the patient at undue risk. In this situation, decision on whether or not to discontinue patients early from trial will depend on the evaluation on a case-by-case basis. Patients who, after evaluation of the above situations are not discontinued from the trial, may have a temporary interruption from trial treatment (see Section 4.4.1). For patients who discontinue early from trial, the assessments will depend on the visit at which it was decided that the patient had to discontinue (see Section 5.4). Patients who discontinue early from the trial within a Treatment Period should perform the planned assessments of the corresponding Treatment Period visit. These patients will not receive any further administration of ARGX-113 during the trial and will return for the ED visit one month (30 ± 2 days) after the last dose administration. An unscheduled visit can be organized if deemed necessary by the Investigator. Patients who discontinue early from the trial between the last visit of a Treatment Period (TP_nV4 or TPE_nV4) and the next Intertreatment Period visit (ITP_nVn or $ITPE_nVn$) should perform the ED assessments one month (30 ± 2 days) after the last dose administration. Patients who discontinue early from the trial at the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments, instead of the ITP_nVn (Part A) or $ITPE_nVn$ (Part B) assessments. Patients who discontinue early from the trial after the ITP (Part A) or ITPE (Part B) visit should perform the ED assessments. Any patient prematurely discontinuing the trial during Part A should perform the EoA/ED assessments according to the General Schedule of Assessments for Part A (Table 1). Any patient prematurely discontinuing the trial during Part B should perform the EoS/ED assessments according to the General Schedule of Assessments for Part B (Table 2).	

Section	Change	Rationale
	All patients are free to withdraw consent from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice to further treatment. Prior to actual withdrawal of consent, an effort should be made to perform a final set of assessments as per the EoA/ED visit in the General Schedule of Assessments for Part A (Table 1) or the EoS/ED visit in the General Schedule of Assessments for Part B (Table 2). Investigators will make and document all efforts made to contact those patients who do not return for scheduled visits.	
4. INVESTIGATIONAL PLAN 4.4. Early Discontinuation 4.4.2. Early Discontinuation from Trial Treatment	Section deleted.	
4. INVESTIGATIONAL PLAN 4.4. Early Discontinuation 4.4.3. Temporary Interruption from Trial Treatment	A patient who does not need to be discontinued early from *trial treatment* might still have a temporary interruption from trial treatment. … Patients for whom treatment is interrupted will have to complete the current Treatment Period and will continue the trial as per General Schedule of Assessments (Table 1). changed to A patient who does not need to be discontinued early from *the trial* might still have a temporary interruption from trial treatment. … Patients for whom treatment is interrupted will have to complete the current Treatment Period and will continue the trial as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). A patient who has had a temporary interruption of trial treatment in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions mentioned above are met.	
4. INVESTIGATIONAL PLAN 4.4. Early Discontinuation	Patients who miss one, two or three infusions per Treatment Period will stay in the trial and will follow the assessments as per General Schedule of Assessments (Table 1). These patients may be eligible for further Treatment Periods during the trial. changed to	See summary above.

Section	Change	Rationale
4.4.4. Missed Doses	Patients who miss one, two or three infusions per Treatment Period will stay in the trial and will follow the assessments as per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). These patients may be eligible for further Treatment Periods during the trial. A patient who has missed doses in Part A may also continue into Part B of the trial and receive (re-)treatment if the conditions in Section 4.4.3 are met.	
5. TRIAL PROCEDURES	Patients should be seen for all visits on the designated days or as closely as possible to the original planned visit schedule. There is a permissible window of ±1 day for Treatment Period visits (Visit 1 to Visit 4), of ±2 days for ITP_nVn, and of ±7 days for the EoS visit (Day 365). Every effort should be made to schedule every visit on the exact day (which is relative to the Baseline visit [SEB or TP_nB]) within the window as described in the General Schedule of Assessments (Table 1). … The SEB will be set at the first trial visit, while the Baseline of each subsequent Treatment Period (TP_nB) will be set at Visit 1 of each corresponding Treatment Period. … The MG-ADL scale needs to be performed prior to the QMG scale. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment. … As from signature of informed consent until EoS, all AEs that occur … Patients who are discontinued early from trial treatment, after they have completed the EoT assessments and, if applicable, the remaining visits of the current Treatment Period, will return every month (30 ± 2 days) for Follow-up visits until Day 365 as per Schedule of Assessments for Patients who Discontinued Early from Trial Treatment (Table 2). These patients will then continue in the trial to be followed for safety and disease severity. changed to Patients should be seen for all visits on the designated days or as closely as possible to the original planned visit schedule. There is a permissible window of ±1 day for Treatment Period visits (Visit 1 to Visit 4), of ±2 days for ITP_nVn (Part A), and of ±7 days for the	

Section	Change	Rationale
	ITPE$_n$Vn (Part B), EoA visit (Day 365) and EoS visit (Day 1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). Every effort should be made to schedule every visit on the exact day (which is relative to the Baseline visit [SEB, or TP$_n$B or TPE$_n$B]) within the window as described in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2). … The SEB will be set at the first trial visit, while the Baseline of each subsequent Treatment Period (*TP$_n$B or TPE$_n$B*) will be set at Visit 1 of each corresponding Treatment Period. … The MG-ADL scale needs to be performed prior to the QMG scale (Part A) as per Table 1. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment (Part A). … As from signature of informed consent until last study visit, all AEs that occur …	
5. TRIAL PROCEDURES 5.2. Treatment Period	… A new Treatment Period can only be started if it can be completed within the 1-year trial duration. changed to 5.2.1. Treatment Period Part A … A new Treatment Period can only be started if it can be completed within the 1-year trial duration of Part A of the trial (re-treatment in Part A can start at the latest on Day 336). Otherwise the patient can be transitioned to Part B after completing the EoA visit. If the patient is not willing or able to continue to Part B, then he/she should continue to the EoA visit.	
5. TRIAL PROCEDURES 5.2. Treatment Period 5.2.1. Treatment Period Part A	Patients who fail to respond to ARGX-113 for three consecutive Treatment Periods will be discontinued from further treatments with ARGX-113 but will remain in the trial to receive appropriate alternative MG therapy. … If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score but cannot complete the entire Treatment Period within the trial duration, the patient should receive appropriate alternative MG therapy and continue to the EoS visit. changed to	

Section	Change	Rationale
	Patients who fail to respond to ARGX-113 for three consecutive Treatment Periods will be discontinued from the trial. … If a patient becomes eligible for (re-)treatment with ARGX-113 per total MG-ADL score but cannot complete the entire Treatment Period within Part A of the trial (re-treatment in Part A can start at the latest on Day 336) then the patient will be transitioned to Part B after completing the EoA visit. If the patient is not willing or able to continue to Part B then he/she should continue to the EoA visit. The transition to Part B can be either $ITPE_0Vn$ or TPE_1V1, depending on the patient status regarding the need for (re-)treatment upon transition from Part A. The first visit in Part B will always coincide with the EoA visit in Part A. The assessments done for the last visit in Part A should not be repeated in Part B.	
5. TRIAL PROCEDURES 5.2. Treatment Period 5.2.2. Treatment Period Part B	Extra section added for Part B: 5.2.2. Treatment Period Part B A Treatment Period will include assessments in 4 weekly visits including treatment with ARGX-113 in eligible patients in need for (re-)treatment. A new Treatment Period can only be started if it can be completed within the trial duration (up to maximum 3 years or until efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first). The following assessments will be performed from Visit 1 to Visit 4 of each Treatment Period: • Assessments of disease severity (MG-ADL scale). (*) • Weight will be measured at Visit 1 and when there is an obvious weight change compared to the last weight assessment.(*) • Vital signs.(*) • Clinical laboratory tests (local labs), only at Visit 1 and Visit 4 of each Treatment Period.(*) • Urinalysis, only at Visit 1 and Visit 4 of each Treatment Period.(*) • Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS), only at Visit 1 and Visit 4 of each Treatment Period.(*) • ADA, only at Visit 1 of each Treatment Period (*)	

Section	Change	Rationale
	• Administration of ARGX-113 as an IV infusion over a period of 1 hour. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring, based on the patient's clinical status. • Review of concomitant medication. • Assess AEs if any. (*) These assessments should be performed prior to administration of ARGX-113 (predose). At Visit 1 of each Treatment Period, the conditions for (re-)treatment will be checked before administration of ARGX-113 (see Section 4.1). Patients may not receive (re-)treatment with ARGX-113 if, at the time of (re-)treatment, they have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. If a patient becomes eligible for (re-)treatment with ARGX-113 but cannot complete the entire Treatment Period within the duration of the trial, the patient should continue to the EoS visit. If the Investigator considers that the patient will not have a clinical benefit from re-treatment then the patient cannot start a new Treatment Period. The patient should then continue to the EoS visit. A change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed, without restrictions, following current medical practice.	
5. TRIAL PROCEDURES 5.3. Intertreatment Period	Intertreatment Period visits occur every 30 days after the previous visit. At each ITP_nVn, an evaluation of the need for (re-)treatment should be done. In case the patient is not in need of (re-)treatment, assessments for ITP_nVn should be performed as listed below and per the General Schedule of Assessments (Table 1). However, in case the evaluation shows that the patient is in need of (re-)treatment and is also eligible for (re-)treatment, the assessments according to TP_nV1 are to be performed instead (see Section 5.2). The following assessments will be performed: changed to	

Section	Change	Rationale
	Intertreatment Period visits occur every 30 days after the previous visit in Part A and every 90 days after the previous visit in Part B. At each ITP_nVn (Part A) or $ITPE_nVn$, (Part B) an evaluation of the need for (re-)treatment should be done. In case the patient is not in need of (re-)treatment, assessments for ITP_nV_n (Part A) or $ITPE_nVn$ (Part B) should be performed as listed below and per the General Schedule of Assessments for Part A (Table 1) or for Part B (Table 2). However, in case the evaluation shows that the patient is in need of (re-)treatment and is also eligible for (re-)treatment, the assessments according to TP_nV1 (Part A) or TPE_nV1 (Part B) are to be performed instead (see Section 5.2). If an ITP visit for Part A is scheduled within 14 days of the EoA visit, then the EoA visit should be performed instead. The following assessments will be performed in Part A:	
5. TRIAL PROCEDURES 5.3. Intertreatment Period	The following text added: The following assessments will be performed in Part B: • Assessments of disease severity (MG-ADL scale). • Vital signs. • Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS). • Review of concomitant medication. • Assess AEs, if any.	
5. TRIAL PROCEDURES 5.4. End of Treatment	Section deleted.	There is no End of Treatment visit.
5. TRIAL PROCEDURES 5.5. Safety and Disease Severity Follow-up Period for Patients who Discontinued Early from Trial Treatment	Section deleted.	In order to reduce the burden on the patients, the safety follow-up period has been replaced by 1 safety follow-up visit.
5. TRIAL PROCEDURES	5.6. End of Study and Early Discontinuation (EoS/ED) Visit	See summary above.

Section	Change	Rationale
5.6. End of Study and Early Discontinuation (EoS/ED) Visit	In case of early discontinuation from the trial, the same assessments as scheduled for EoS (Day 365) must be performed as follows: • Assessments of disease severity. … (*) • …(*) (*) Only applicable for patients following Table 1. changed to 5.5. End of Part A, End of Study and Early Discontinuation (EoA/ED or EoS/ED) Visit In case of early discontinuation, the same assessments as scheduled for EoA (Day 365) or EoS (Day 1095 or when efgartigimod becomes commercially available or another option to access efgartigimod is available, whichever option comes first) must be performed as follows: For EoA/ED (Part A): • Assessments of disease severity. … • … For EoS/ED (Part B): • Assessments of disease severity (MG-ADL scale) should be performed prior to any other assessments except for the weight assessment. • Physical examination. • Weight. • Vital signs. • Clinical laboratory tests (local labs). • Urinalysis. • Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS). • ADA (only in case of ED). • Review of concomitant medication. • Assess AEs, if any.	Part B allows for freedom of changing therapy and there will be no restrictions on the type of therapy that can be used and no prohibited medications. This is because Part B will shift to a more real-life approach.
6. TRIAL TREATMENT 6.8. Prior Treatments and Concomitant Medications	The following medications or treatments will lead to discontinuation from treatment *during the trial* as from SEB onwards: changed to	

Section	Change	Rationale
6.8.1. Prohibited Medications during the Trial	The following medications or treatments will lead to discontinuation from treatment *during Part A of the trial* as from SEB onwards:	
6. TRIAL TREATMENT 6.8. Prior Treatments and Concomitant Medications 6.8.1. Prohibited Medications during the Trial	The following text added: In Part B of the trial, a change of the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is allowed without restrictions, following standard clinical practice. PLEX, IVIg, immunoadsorption or use of a new type of corticosteroid or an increased dose of the current corticosteroids used as stand-alone therapy or in combination is also allowed in Part B.	
6. TRIAL TREATMENT 6.9. Medical Care of Patients after End of Study	Sentence deleted: … The Sponsor will not provide any additional care to these patients, neither will ARGX-113 be provided on a compassionate use program.	The aim of the extension is to provide the patients with the chance to have access to efgartigimod while it is not yet commercially available or available through another patient program. Therefore this sentence is no longer valid.
6. TRIAL TREATMENT 6.11. Handling Missed Doses of Investigational Medicinal Product	… according to the General Schedule of Assessments (Table 1). … changed to … according to the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2). …	See summary above.
7. TRIAL ASSESSMENTS 7.1. Monitoring of Disease Severity	Monitoring of disease severity will be assessed using MG-ADL and QMG. Both assessments have to be performed predose on all ARGX-113 infusion days and prior to any other assessment at each visit except for the assessment of weight (if applicable) and signing of the ICF at SEB. The MG-ADL scale needs to be performed prior to the QMG scale (Table 1). changed to Monitoring of disease severity will be assessed using MG-ADL (Part A and B) and QMG (Part A only). The assessments, where applicable, have to be performed predose on all ARGX-113 infusion days and prior to any other assessment at each visit, except for the assessment of weight (if applicable) and signing of the ICF at SEB. The MG-ADL scale needs to be performed prior to the QMG scale in Part A (Table 1).	

Section	Change	Rationale
7. TRIAL ASSESSMENTS 7.1. Monitoring of Disease Severity 7.1.1. Myasthenia Gravis Activities of Daily Living	... It evaluates the capacity to perform different activities of daily living such as talking, chewing, swallowing, breathing, brushing the teeth/combing the hair, or arising from the chair and it also assesses double vision and eyelid droop. changed to …It evaluates the capacity to perform different activities of daily living such as talking, chewing, swallowing, breathing, brushing the teeth/combing the hair, or rising from a chair and it also assesses double vision and eyelid droop.	Sentence corrected.
7. TRIAL ASSESSMENTS 7.2. Safety	Safety assessments will consist of monitoring and recording all AEs, pregnancies, *suicidality assessment,* safety laboratory testing, measurement of vital signs, *ECGs,* physical examinations; … changed to Safety assessments will consist of monitoring and recording all AEs, pregnancies, *suicidality assessment (Part A only),* safety laboratory testing, measurement of vital signs, *ECGs (Part A only),* physical examinations; …	See summary above.
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.1.2. Reporting of Adverse Events and Serious Adverse Events	All AEs that occur during the trial from signature of the ICF until *EoS* are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF. … changed to All AEs that occur during the trial from signature of the ICF until *the last study visit* are to be recorded on the appropriate AE pages (either 'serious' or 'non-serious') in the eCRF.	
	Additional text added: All SAEs that are spontaneously reported within 30 days after the last trial visit are to be collected and reported as previously described and all efforts should be made to follow-up until resolution.	In order to comply with generally accepted safety pharmacovigilance guidelines, this paragraph has been added.
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.1. Adverse Events 7.2.1.4. Follow-up of Adverse Events and	Any AEs observed from signing the ICF to *the EoS visit* will be followed up to resolution, … … All SAEs that are spontaneously reported after *the EoS visit* are to be … changed to	See summary above.

Section	Change	Rationale
Serious Adverse Events	Any AEs observed from signing the ICF to *the last study visit* will be followed up to resolution, … … All SAEs that are spontaneously reported after *the last study visit* are to be …	
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.1. Adverse Events 7.2.1.5. Reporting and Follow-up Requirements for Pregnancies	Urine pregnancy tests will be conducted and analyzed locally at all visits as detailed in the General Schedule of Assessments (Table 1). changed to Urine pregnancy tests will be conducted and analyzed locally at visits as detailed in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2). Results will be recorded in the eCRF.	
7.2.1.5.1. Pregnancies in Female Patients	• The patient should have EoT assessments. • All assessments for EoT (see Sections 4.4.2 and 5.4) must be performed unless contraindicated by pregnancy … changed to • The patient should have the planned ED assessments. • All planned assessments (see Sections 4.4.2 and 5.4) must be performed unless contraindicated by pregnancy …	There is no End of Treatment visit.
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.2. Clinical Laboratory Evaluations	Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, PD, and ADA will be analyzed at a central lab as indicated in the General Schedule of Assessments (Table 1) and Appendix 3. Patients need to be fasting for at least 8 hours prior to the sampling for clinical laboratory tests as from SEB up to EoS. Patients need to be fasting for at least 8 hours prior to the sampling for clinical laboratory tests as from SEB up to EoS. … For all patients of childbearing potential, a urine pregnancy test will be conducted and analyzed locally at the site (on the urine samples taken for urinalysis) at all visits (Table 1). The estimated total maximum blood volume needed for a patient during the trial (when completing the trial up until the last visit) is between 170 mL for a patient who receives 1 Treatment Period only and 362 mL for a patient who receives a maximum of 6 Treatment Periods.	See summary above.

Section	Change	Rationale
	Besides the urine pregnancy test, which will be conducted and analyzed locally, all samples will be analyzed centrally. changed to In Part A blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be analyzed at a central laboratory. PD and ADA will be analyzed at a specialty laboratory as indicated in the General Schedule of Assessments for Part A (Table 1) and Appendix 3. Patients need to be fasting for at least 8 hours prior to the sampling for clinical laboratory tests as from SEB up to EoA. In Part B, blood and urine samples for determination of clinical chemistry, hematology and urinalysis will be analyzed at local laboratories and results will not be recorded in the eCRF. Blood samples for ADA will be analyzed at a specialty laboratory as indicated in the General Schedule of Assessments for Part B (Table 2) and Appendix 3. … For all patients of childbearing potential, a urine pregnancy test will be conducted and analyzed locally at the site (on the urine samples taken for urinalysis, if applicable) at all visits in Part A (Table 1) and at Visit 1 and 4 of each Treatment Period, at ITPE visits, at EoS/ED and at the discretion of the Investigator in Part B (Table 2). The estimated total maximum blood volume needed for a patient during Part A of the trial (when completing the trial up until the last visit) is between 170 mL for a patient who receives 1 Treatment Period only and 362 mL for a patient who receives a maximum of 6 Treatment Periods. The estimated total maximum blood volume needed for a patient during Part B of the trial (when completing the trial up until the last visit) is between 24 mL for a patient who receives 1 Treatment Period only and 100 mL for a patient who receives 6 Treatment Periods.	
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.3. Vital Signs, Physical Examination, and ECG	Assessment of vital signs (supine blood pressure, heart rate, and body temperature), physical examination and ECG will be performed at the time points indicated in the General Schedule of Assessments (Table 1) (predose at dosing days). A 12-lead ECG will be recorded locally as per local regulations …	

Section	Change	Rationale
	changed to Assessment of vital signs (supine blood pressure, heart rate, and body temperature), physical examination and ECG (Part A only) will be performed at the time points indicated in the General Schedule of Assessments for Part A (Table 1) and for Part B (Table 2) (predose at dosing days).	
	Weight will be measured at SEB, at the EoS/ED visit, and can be repeated … changed to Weight will be measured at SEB, at the EoA/ED visit, at Visit 1 of Part B, at the EoS/ED visit, and can be repeated … A 12-lead ECG will be recorded locally (only for Part A) as per local regulations …	
7. TRIAL ASSESSMENTS 7.2. Safety 7.2.4. Suicidality Assessment	As is recommended …suicidal ideation and behavior will be included in this clinical trial. changed to As is recommended … suicidal ideation and behavior will be included in this clinical trial (Part A only).	
7. TRIAL ASSESSMENTS 7.3. Pharmacodynamics	The PD markers (total IgG and IgG subtypes [IgG1, IgG2, IgG3 and IgG4], and … changed to In Part A, the PD markers (total IgG and IgG subtypes [IgG1, IgG2, IgG3 and IgG4], and …	
7. TRIAL ASSESSMENTS 7.4. Anti-Drug Antibodies	Blood samples to assess ADA will be collected predose at the time points as indicated in Table 1. At Baseline (SEB and TP_nB), confirmatory and titer analysis … changed to Blood samples to assess ADA will be collected predose at the time points as indicated in Table 1 and Table 2. At Baseline (SEB, TP_nB and TPE_nB), confirmatory and titer analysis …	
8. STATISTICS	Wording added: Endpoints will be summarized by treatment (as received in ARGX-113-1704).	Wording added for clarification.
8. STATISTICS	A tabular presentation of the patient disposition will be provided. It will include the number of *patients*	Wording corrected; statistical analysis will be carried out

Section	Change	Rationale
8.3. Patient Disposition, Characteristics and Concomitant Medication	*screened*, enrolled, completed *(per Treatment Period),* … … A list of protocol violations will be identified and discussed with the Investigator to categorize as major or minor and the same will be reported. … Use of concomitant medication will be *summarized by treatment* with frequency and percentage. All concomitant medications used will be listed. changed to A tabular presentation of the patient disposition will be provided. It will include the number of *patients* enrolled, completed (*by cycle*), … … Use of concomitant medication will be *summarized* with frequency and percentage. All concomitant medications used will be listed.	per cycle (Treatment Period + Intertreatment Period) not just per Treatment Period. The protocol violation process is not relevant for the statistics in this section.
8.4. Statistical Methods 8.4. Statistical Methods 8.4.1. Primary and Secondary Endpoint Analyses	Frequency tables will be made for all binary variables, i.e., AEs, for all available time points, by Treatment Period (including Intertreatment Period) and overall. Summary statistics will be provided for the continuous endpoints (e.g., laboratory values, vital signs, ECGs) in terms of absolute values and changes from SEB (for 1-year assessment), and changes from Treatment Period Baseline (TP_1B), at each Treatment Period (including Intertreatment Period),by cycle and available time points. changed to Frequency tables will be made for all binary variables, i.e., AEs, by cycle and overall. Summary statistics will be provided for the continuous endpoints (e.g., laboratory values, vital signs, ECGs) in terms of absolute values and changes from TP_1B by cycle and available time points.	Corrected to reflect that AEs are not reported by timepoint and that for safety endpoints only changes from the treatment period baseline of the first cycle will be summarized as patients might start the study with an intertreatment period.
8. STATISTICS 8.4. Statistical Methods 8.4.2 Tertiary Endpoint Analyses	The tertiary endpoints will be analyzed in a descriptive manner. Summary statistics will be provided for the continuous endpoints (e.g., total MD-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies) in terms of absolute values and changes from SEB (for 1-year assessment)	Corrected to reflect that changes from the treatment period baseline of the first cycle will be summarized (instead of changes from SEB) as patients might start

Section	Change	Rationale
	and changes from TPB, at each Treatment Period (including Intertreatment Period), and available time points. For levels of total IgG and subtypes and also anti-AChR/anti-MuSK antibodies, the percentage change from SEB and from TPB will also be presented. Every 30 days' percent change compared to SEB will be calculated. Frequency tables will be made for incidence of ADA to ARGX-113 every 30 days in patients who are (re-)treated with ARGX-113, at SEB, at Visits 1 and 4 of each Treatment Period, and at the EoS visit. In addition, within each Treatment Period, the proportion of patients treated with ARGX-113 that present ADA's over all time points will be calculated together with 95% confidence interval (CI) using Clopper-Pearson exact method. Interim analyses might be performed to support questions for authorities and/or submissions. changed to The tertiary endpoints will be summarized descriptively. Summary statistics will be provided for the continuous endpoints (e.g., total MD-ADL score, total QMG score, levels of total IgG and subtypes, anti-AChR/anti-MuSK antibodies) in terms of absolute values, changes from TP_1B or changes from TP_nB, by cycle and available time points. For levels of total IgG and subtypes and also anti-AChR/anti-MuSK antibodies, the percentage change from TP_1B and from TP_nB will also be presented. Frequency tables will be made for incidence and prevalence of ADA to ARGX-113. 8.5. Interim Analyses Interim analyses might be performed to support questions for authorities and/or submissions.	the study with an intertreatment period. ADA will also be summarized as is consistent with the literature. An extra section has been added for interim analyses as these do not belong with the tertiary endpoints.
Appendix 3: Laboratory Evaluations	Note: All blood and urine samples will be collected locally (predose on dosing days) and analyzed centrally. changed to Note: For Part A, all blood and urine samples will be collected locally (predose on dosing days) and analyzed at a central or specialty laboratory. For Part B, blood and urine samples for clinical chemistry, hematology and urinalysis will be analyzed locally,	Given the long time frame of the extension and the option of unscheduled visits being carried out at the request of the Investigator, the more flexible option of working with a local laboratory has been chosen over the central laboratory structure.

Section	Change	Rationale
	while ADA samples will be analyzed in a specialty laboratory.	
Appendix 4 Administrative Structure	Clinical Laboratories changed to Clinical Laboratories (Part A only)	
Appendix 5 Decision Tree for re-Treatment (Part A)	Appendix 5 Decision Tree for re-Treatment (Part A) changed to Appendix 5 Decision Tree for re-Treatment in Part A (Part 1)	Title changed to avoid confusion with Part A and Part B of the trial.
Appendix 6 Decision Tree for re-Treatment (Part B)	Appendix 6 Decision Tree for re-Treatment (Part B) changed to Appendix 6 Decision Tree for re-Treatment in Part A and Part B (Part 2)	Title changed to avoid confusion with Part A and Part B of the trial.
	Figure adapted to include re-treatment scenario for Part B.	Figure adapted to include the re-treatment scenario for Part B of the trial.
Appendix 7 Summary of Changes	New appendix created for Summary of Changes.	Due to the number of changes, and therefore the size of the tables required to describe all the changes made to the protocol, the detailed Summary of Changes tables have been moved to Appendix 7.

Protocol Version 1.0 compared to Protocol Version 2.0

Changes from Protocol Version 1.0 compared to Protocol Version 2.0 are summarized below.

Of note: updates of headers/footers and tables of contents as well as editorial changes regarding layout, font, and format are not captured in this summary.

Section	Change	Rationale
SIGNATURES OF SPONSOR	"[redacted]" changed to "[redacted]"	[redacted] was replaced by [redacted]
SYNOPSIS ROLL-OVER	"Patients who discontinued early from trial ARGX-113-1704 or discontinued early from randomized treatment for rescue or pregnancy reasons or for a	Change of wording to clarify that there needs to be a

4.1. Summary of Trial Design ROLL-OVER	(serious) adverse event ([S]AE) that might jeopardize the safety of the patient in that trial will not be offered the option to roll over into this trial." changed to "Patients who discontinued early from trial ARGX-113-1704 or discontinued early from randomized treatment for rescue or pregnancy reasons or for a serious adverse event (SAE) that is likely to result in a life-threatening situation or pose a serious safety risk in that trial will not be offered the option to roll over into this trial."	serious safety risk in order to have the patient discontinued.
SYNOPSIS (RE-)TREATMENT 4.1. Summary of Trial Design (RE-)TREATMENT	"Each patient may start a (new) Treatment Period with ARGX-113 when all the following criteria apply: The patient has completed the previous Treatment Period; AND" changed to: "Each patient will start a (new) Treatment Period with ARGX-113 when all the following criteria apply: The patient has completed the previous Treatment Period (i.e. after Visit 4); AND"	Wording adjusted for clarification.
SYNOPSIS (RE-)TREATMENT 4.1. Summary of Trial Design (RE-)TREATMENT	"Patients who are in need of an additional treatment but who are not eligible to receive (re-)treatment for reasons listed here will remain in the trial to receive appropriate alternative MG treatment." changed to: "Patients who are in need of an additional treatment but who are not eligible to receive (re-)treatment for reasons listed here will remain in the trial to receive appropriate alternative MG treatment see Appendix 5 and Appendix 6." "Patients who fail to respond to ARGX-113 ..." changed to: "Patients who show a treatment failure to ARGX-113 ..."	Wording adjusted for clarification.
SYNOPSIS STANDARD of CARE (SoC) 4.1. Summary of Trial Design STANDARD OF CARE (SoC)	Addition of the following sentences: "Permitted SoC for MG treatment under this protocol include NSIDs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as acetylcholinesterase (AChE) inhibitors."	Sentences added for extra clarification.

	"In case these medications are taken for another indication than MG, same conditions apply." "Administration of AChE inhibitors must be halted for at least 12 hours prior to performing the QMG assessment. Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC."	
SYNOPSIS RESCUE THERAPY 4.1. Summary of Trial Design RESCUE THERAPY	"If necessary, patients may receive rescue therapy, which will be limited to plasma exchange (PLEX), ..." changed to: "Rescue therapy, will be limited to plasma exchange (PLEX, ..."	Wording adjusted to enhance clarification.
	"In situations where rescue therapy is given, patients will be discontinued early from trial treatment." changed to "In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from trial treatment."	
SYNOPSIS Inclusion Criteria 4.3.1 Inclusion Criteria	Criterion no. 3: "*Note: AChE inhibitors must be held for at least ...*" changed to "*Note: AChE inhibitors must be halted for at least ...*" Deletion of the following sentence: "Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC."	Administrative change.
SYNOPSIS Exclusion Criteria 4.3.2 Exclusion Criteria	Criterion no. 5: "Patients with known autoimmune disease other than MG (i.e., autoimmune thyroiditis) that …" changed to "Patients with known autoimmune disease other than MG (for example autoimmune thyroiditis, rheumatoid arthritis, …) that …"	Typo/wrong use of "i.e." was corrected, additional example provided.
SYNOPSIS Exclusion Criteria 4.3.2 Exclusion Criteria	New exclusion criterion added: 7. "Patients with known medical history of hypersensitivity to any of the ingredients of ARGX-113."	Updated in order to align with CTP ARGX-113-1705 Japan-specific version 1.1 which was updated upon request of PMDA.

Table 1 General Schedule of Assessments	Assessment "Weight" changed to "Weight and Height"	Updated in order to align with ARGX-113-1705 SAP.
	Addition of the following sentence in footnote "i" "Height will be measured at SEB."	Added for completeness.
	"[d] During the UNS visit, additional assessments can be performed at …" changed to "[d] During the UNS visit, additional assessments as indicated in the SoA can be performed at …"	Administrative change.
DEFINITION OF TERMS	Childbearing potential: Deletion of the following sentence: "Determination of FSH levels can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy if the test result is within the postmenopausal range per the central laboratory performed in study ARGX-113-1704."	Correction.
4.4.2. Early Discontinuation from Trial Treatment	"□ Patient develops an (S)AE that might jeopardize the safety of the patient." changed to: "□ Patient develops an SAE that is likely to result in a life-threatening situation or pose a serious safety risk."	Change of wording to clarify that there needs to be a serious safety risk in order to have the patient discontinued.
4.5. Protocol Deviations	"The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC), except …" changed to "The Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of an amendment from the IRB/IEC and Regulatory Authority as per local regulation, except ..."	Administrative change.
4.7. End of Trial Definition	The following was added: "4.7. End of Trial Definition End of trial is defined as last patient last visit."	Added for completeness (was missing in the previous version).

5.1. Informed Consent and Roll-Over Visit	"□ Weight" changed to "□ Weight and height"	
6.8. Prior Treatments and Concomitant Medications	Addition of the following sentence: "Vaccines (except for live/live-attenuated vaccines) will be allowed during the trial when administered at least 48 hours pre-infusion or 48 hours postinfusion of IMP."	For patient safety, allowing for vaccines to be administered according to common clinical practice and to reduce the risk of confusing vaccination-related adverse events (such as fever) with IMP-infusion related adverse events.
6.8.1. Prohibited Medications during the Trial	"The following medications or treatments will not be permitted as from signing the ICF during the trial:" changed to "The following medications or treatments will lead to discontinuation from treatment during the trial as from SEB onwards:"	Wording updated for clarification.
6.8.1. Prohibited Medications during the Trial	"an increase of the dose/frequency of SoC, even if used for indications other than MG" changed to "a change in the type or an increase of the dose/frequency of SoC, even if used for indications other than MG"	Clarify that patients are not to start treatment with a new SoC
	"Vaccines" changed to "Live/live-attenuated vaccines"	For patient safety, allowing for vaccines to be administered according to common clinical practice and to reduce the risk of confusing vaccination-related adverse events (such as fever) with IMP-infusion related adverse events.
	"Rescue therapy" changed to "Rescue therapy when used in patients who meet the criteria to be rescued"	Wording added for clarification.
	Additional bullet: "□ Use of PLEX or immunoadsorption more than once during the study period"	

6.8.2. Rescue Therapy	First sentence ("If necessary, patients may receive rescue therapy if their gMG deteriorates.") deleted.	To align with the corresponding section in the Synopsis, Section 4.1, and Section 6.8.1.
	"In situations where rescue therapy is given, patients will be discontinued early from trial treatment." changed to "In situations where the treatments as listed above are given under the protocol-defined rescue criteria, patients will be discontinued early from the trial treatment."	
6.11. Handling Missed Doses of Investigational Medicinal Product	"In case a dose needs to be delayed for more than 5 days, …" changed to "In case a dose needs to be delayed for more than 3 days, …"	Correction.
7.1.2. Quantitative Myasthenia Gravis	End of section, one but last sentence: "…dynamometer, and is based on physician's examination." changed to "…dynamometer, and is based on the trained rater's examination."	Updated because the rater needs to be a trained person, but not necessarily a physician.
7.2.1.1. Adverse Events of Special Interest	New section added: "An AESI (serious or non-serious, related or not related) is an event of scientific and medical concern specific to the sponsor's product or program. ARGX-113 treatment induces reductions in IgG levels, and there is a potential risk for infections associated with the low IgG levels. As such, any infection will be considered AESI in this trial. Further characterizing information will be collected in the eCRF, such as: location of infection, relationship to underlying condition, medical history and concomitant medication, reoccurrence of previous infection, previous rescue therapy, any confirmatory procedure, culture or urgent medical intervention."	Since the mechanism of action of ARGX-113 induces reductions in IgG levels there is a potential of infection risk. Therefore, infections will be captured as AESIs, in order to collect the data in a systematic way.
7.2.1.4. Follow-up of Adverse Events and Serious Adverse Events	Second paragraph: "Every effort should be made to follow all AEs …" changed to "Every effort should be made to follow all (S)AEs …"	Table deleted and text updated to clarify that all SAEs are to be followed-up until resolution.
	Sentence referring to Table 3 and Table 3 deleted	

7.2.1.5.1 Pregnancies in Female Patients	The following sentence has been added: "If required by local regulations, the female participant will be requested to sign a separate pregnancy ICF."	Added for completeness.
7.2.2. Clinical Laboratory Evaluations	"Refer to Appendix 4 for the addresses of the laboratories used for sample analyses." changed to "Refer to Appendix 4 for the addresses of the laboratories used for sample analyses and storage."	Updated in order to align with CTP ARGX-113-1705 The Netherlands-specific version 1.2.
7.3. Pharmacodynamics	"(PD)" was added to the section title.	Added for completeness.
7.4. Anti-Drug Antibodies	"(ADA)" was added to the section title.	
10.2. Ethical Conduct of the Trial	The paragraph: "This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2008), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted." was updated to: "This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted. To comply with the Declaration of Helsinki (2013), argenx is assessing the appropriateness and possibility of making the study drug available for clinical study participants post-trial."	Updated in order to align with CTP ARGX-113-1704 The Netherlands-specific amendment version 1.1. upon request of the Ethics Committee of The Netherlands.
11.1. Data Handling and Record Keeping	First sentence: "It is the Investigator's responsibility to maintain essential trial documents (including regulatory documents, eCRFs, signed patient ICFs, source documents, …" changed to "It is the Investigator's responsibility to maintain essential trial documents (including records and documents pertaining to the conduct of this trial and the distribution of IMP, regulatory documents, eCRFs, signed patient ICFs, laboratory test results, IMP inventory records, source documents, …"	Updated to avoid duplication of information.

	The following sentence was added to the end of the first paragraph: "The Sponsor will notify the Principal Investigator of these events."	
11.1. Data Handling and Record Keeping	Third paragraph ("The United States (US) Food and Drug Administration (FDA) regulations … the Principal Investigator of these events.") deleted.	Updated to avoid duplication of information.
Appendix 3 Laboratory Evaluations	Other: "follicle-stimulating hormone (FSH) test" deleted	Correction (FSH test does not need to be redone in this trial).
Appendix 4 Administrative Structure	Clinical Laboratories: "Asia Covance Asia Pte Ltd1 International Business Park #01-01 The Synergy Singapore 609917" deleted	This Covance Lab is not involved anymore in the trial since Korea is dropped from country mix.
	"Analysis of Pharmacokinetics-Pharmacodynamics (PK-PD), Anti-Drug Antibodies (ADA)" changed to "Analysis of Pharmacodynamics (PD), Anti-Drug Antibodies (ADA)"	Correction (PK is not performed in this trial).
	Addition of the following: "Long-Term Storage of Pharmacodynamics (PD), Anti-Drug Antibodies (ADA) Brooks Life Science, Biostorage Technologies GmbH Im Leuschnerpark 1b 64347 Griesheim Germany"	Updated in order to align with CTP ARGX-113-1705 The Netherlands-specific version 1.2.
Appendix 5 Decision Tree for re-Treatment (Part A)	Figure added.	Added for clarification.
Appendix 6 Decision Tree for re-Treatment (Part B)	Figure added.	

APPENDIX 8: Temporary Changes to Study Procedures in ARGX-113-1705 Related to the COVID-19 Pandemic

Introduction

As the COVID-19 pandemic poses issues for both sites and patients and presents unprecedented challenges in uncharted territory, this crisis prompted the sponsor to perform a critical review of both efgartigimod administration and changes needed to the study in order to safeguard patient safety, while still being able to gather additional data.

The risk/benefit, safety profile, guidance for site conduct in terms of visits and assessments, as well as data entry, and potential changes in the Schedule of Assessments are included below.

Safety of Efgartigimod: Mechanism of Action, Pharmacodynamics and Risk/Benefit in Patient Safety

Efgartigimod administration results in a targeted reduction in levels of all IgG subtypes. However, and more importantly, it does not impact levels of other immunoglobulin isotypes, such as IgA and IgM. Other elements of the immune system are not impacted by efgartigimod treatment.

Efgartigimod induces a targeted reduction of IgG levels, without impacting IgG production. The maximum mean reduction in total IgG is approximately 70%; therefore, residual IgG and other immunoglobulin levels remain constant during treatment. It is therefore anticipated that patients can mount an immune response. In support of this, experiments in FcRn knockout animals and in animals treated with FcRn antagonist demonstrated that a specific immune response was obtained following an antigen trigger, albeit with reduced (antigen-specific) IgG titers. Additionally, after ceasing efgartigimod treatment, IgG recycling returns and total IgG levels increase and return to baseline levels within a few weeks.

Looking at administration in humans, efgartigimod treatment at doses ≥10 mg/kg have been administered to more than 120 healthy volunteers and patients with generalized myasthenia gravis (gMG), immune thrombocytopenia, and pemphigus in studies carried out prior to phase 3 studies. No general or infection-related safety concerns were identified.

The phase 3 ADAPT gMG study enrolled 167 patients and data will be available in mid-2020. An active assessment of adverse event reports during the study remains ongoing. Although the phase 3 ADAPT data are blinded, no safety concern has been identified to date.

Available data from trials of other FcRn antagonists have not identified any increased risk of infection.

ADAPT/ADAPT+: Pre-existing Safety Measures and Changes to Be Implemented in the Current Situation

The phase 3 ADAPT study implements multiple layers of safety measures and reporting. Efgartigimod is administered in treatment cycles, in which 4-weekly infusions are followed by additional treatment cycles that are administered according to clinical need. Therefore, during the

follow-up period after each treatment cycle, FcRn recycling resumes and IgG levels begin to increase.

The protocol gives guidance to temporarily or permanently discontinue treatment when the patient has signs of clinically significant of bacterial, viral, or fungal infection, in order to treat the underlying condition. The treatment can be initiated at a later time once the clinically significant infection has been deemed resolved. A Treatment Period can be considered as interrupted if the patient is not able to visit the site for more than 1 visit. In such cases, a new Treatment Period can be initiated at a later date.

Additionally, any case of infection is regarded as an adverse event of special interest (AESI) and is subject to structured safety reporting with standardized questions in the eCRF.

The current COVID-19 situation warrants new measures to be introduced for patient safety. These measures will allow patients to be evaluated remotely if/when quarantine is imposed. For example, any remaining visits in an interrupted Treatment Period, may be performed remotely, in cases where the patient is not allowed or cannot physically visit the site. These measures respect both patient safety and local guidance, as well as allowing basic safety data to be collected.

The assessments identified for telephone assessment visits are highlighted with the use of bold italics in the existing Schedule of Assessments for Part A in Table 1 and for Part B in Table 2. Guidance on the execution of these visits and assessments is given below.

By providing a structured back-up plan, we aim to mitigate the risks of the COVID-19 pandemic, while still respecting both patient safety and collection of safety data and remaining compliant with GCP.

Visits with the possibility of remote assessment by telephone:

TP_xV2, TPE_xV2, TP_xV3, TPE_xV3, TP_xV4, TPE_xV4, ITP_xVx, $ITPE_xVx$, EoA, EoS, ED, and UNS. See the Schedule of Assessments for Part A (Table 1) and for Part B (Table 2).

Treatment Period visits will be replaced by telephone assessment visits during the current COVID-19 situation when the Treatment Period is considered interrupted.

Mandatory physical visits:

Initiating a new Treatment Period can only be done when the patient is physically on site.

Guidance to Sites in Case of Suspected COVID-19 in Patients

As sponsor we want to emphasize and highlight the need to follow the guidance issued by local authorities. Wherever guidance is unclear, or if no specific guidance is available, argenx will recommend to either postpone the visit if possible or evaluate the need for telephone assessments to replace a physical visit.

The site should contact the patient prior to each visit, and conduct the following COVID-19 assessments:

1. Does the patient have symptoms, such as cough, fever, muscle pain, shortness of breath*?

- If NO: Go to Questions 2 and 3.

- If YES:

• The patient should be tested for COVID-19:

The investigator needs to document a positive COVID-19 test as an AESI. The anonymized result needs to be sent to the sponsor for filing. If COVID-19 safety measures are stopped according to local regulations, COVID-19 tests should continue to be performed and the results sent to the sponsor.

*Shortness of breath includes an otherwise unexplained deterioration in the patient's MG-ADL score for breathing. In cases where the MG-ADL score for breathing is 2 or 3 additional COVID-19 testing should be carried out. The exception to this is when a patient has an MG-ADL score for breathing of 2 at baseline. In such cases the patient should only be tested when the MG-ADL score for breathing returns to 2 after previous improvement or when it deteriorates to 3.

The visit will only take place once the patient has a negative test for COVID-19. The planned visit may need to be rescheduled or **can be replaced by a telephone assessment visit**. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **Remaining visits in the Treatment Period can be performed as telephone assessment visits.**

• If the patient is tested and found to be COVID-19 negative:

The patient can come to the next visit as scheduled. Follow-up of the patient should be done according to the protocol (decision to be taken if treatment can be given or is to be postponed).

• If the patient is tested and found to be COVID-19 positive:

The patient can only come to the site once he/she has a negative test for COVID-19, and so the planned visit may need to be rescheduled or replaced by a telephone assessment visit. If the patient was in a treatment cycle, the treatment will have to be interrupted. A new treatment cycle may be initiated later. **The remaining visits in the Treatment Period can be replaced by telephone assessment visits.**

2. The patient has no Corona-like symptoms and is not aware of any contact he/she may have had with someone who tested positive for COVID-19:

• The visit can proceed as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

3. The patient has no Corona-like symptoms but has been in contact with someone who tested positive for Corona virus:

• If the contact was 14 days or longer before the study visit => the visit can go ahead as planned. If the patient cannot physically come to the clinic due to the local COVID-19 situation, the visit can be replaced by a telephone assessment visit.

• If the contact was less than 14 days before the study visit => the visit needs to be rescheduled at least 14 days after the contact occurred or be replaced by a telephone assessment visit.

How to: Information related to study procedures and data collection

The assessments deemed suitable for telephone consultation are:

- Re-consenting where warranted, MG-ADL, Adverse Event and Concomitant Medication questioning.

Since QMG needs quantification by the physician, using specific equipment, such as a dynamometer and spirometer, this assessment is not deemed suitable for telephone assessment.

Telephone consultation will allow safety data to be collected and to check on the patient's well-being, while the derived MG-ADL score may give an indication of the need for another treatment with efgartigimod.

Re-consenting with the updated ICF, or consent to Part B of the ADAPT+ study can be done remotely in view of the COVID-19 situation.

Options for consent might entail:

- physical signature by sending the ICF to the patient by courier and having a phone call with the patient, then having the signed document sent back to the site.
- phone call with the patient, asking for email confirmation to corroborate verbal consent.
- organize a conference call or video call together with the patient and impartial witness, where needed.
- if no phone call or video call is possible, email documented consent.

Depending on regional requirements the options can be limited, after consultation with the relevant IRB/IEC and/or regulatory authority.

Data collected during a telephone assessment visit can be entered into the e-CRF pages of the corresponding "missed" visit. Enter the date of the phone call as the "date of visit" and enter the data obtained in the applicable CRF pages. For the assessments that are not performed, answer "no" to the question if the assessment was made in the respective forms. Add "COVID-19 telephone" in the comment section of the CRF.

If you are not able to contact the patient, inactivate the full study visit in the CRF and confirm the missing visit in the comments section as "COVID-19."

Other than conducting telephone assessments, there may be other changes in the current practice on site. Halting spirometry in COVID-19 patients may be required, or only allowing use of a dedicated spirometry device (for contamination reasons). There can be a temporary halt in performing this assessment, or conducting a partial assessment is also permitted.

In order to give a clear overview of protocol deviations related to the specific COVID-19 situation, dedicated protocol deviations with the COVID-19 label have been created to which any missed visit or assessment can be attributed.

APPENDIX 9: Contraceptive and Barrier Guidance

Definitions

Woman of childbearing potential

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

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

Contraception Guidance

Female Contraception for Women of Childbearing Potential

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

The following methods are considered highly effective methods of contraception:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation

– Oral

– Intravaginal

– Transdermal

2. Progestogen-only hormonal contraception associated with inhibition of ovulation

– Oral

– Injectable

– Implantable

3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

The following methods are considered acceptable methods of contraception:

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

Male Contraception

An acceptable method of contraception is a condom.