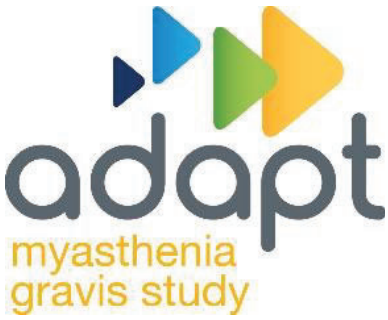
Clinical Trial Protocol



Protocol Title:	**A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness**
Protocol Number:	**ARGX-113-1704 (ADAPT)**
Date of Protocol:	**11 July 2019, Version 3.0, Final**
Product:	**ARGX-113**
IND No:	CCI
EudraCT No:	**2018-002132-25**
Trial Phase:	**3**
Sponsor:	**argenx BVBA** **Industriepark Zwijnaarde 7** **B-9052 Zwijnaarde** **BELGIUM** **Phone:** PPD
Medical Director:	PPD **argenx BVBA** **Industriepark Zwijnaarde 7** **B 9052 Zwijnaarde** **BELGIUM** **Phone:** PPD PPD

Contract Research Organization (CRO):	**Syneos Health™ group company including INC Research, LLC, together with INC Research UK Limited** **3201 Beechleaf Court** **Suite 600** **Raleigh, North Carolina 27604-1547** **US** **Phone:** PPD

The following additional numbers are also available for urgent contact

24 Hour Urgent Medical Helpline Number:	PPD

For drug safety reporting, contact the below e-mail address

Safety Mailbox/Fax:	PPD

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.

SIGNATURES OF SPONSOR

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness

PROTOCOL NO: ARGX-113-1704 (ADAPT)

SPONSOR REPRESENTATIVE

PPD

7/11/2019

---------- ----------

PPD **Signature** **Date**

PPD **argenx BVBA**

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Trial to Evaluate the Efficacy, Safety and Tolerability of ARGX-113 in Patients with Myasthenia Gravis Having Generalized Muscle Weakness

PROTOCOL NO: ARGX-113-1704 (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	28 November 2018
Protocol Version 3.0	11 July 2019

SUMMARY OF CHANGES

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 captured in this summary.

Section	Change	Rationale
SIGNATURES OF SPONSOR	PPD	PPD
SYNOPSIS Criteria for Evaluation: Secondary Endpoints 3.2. Secondary Endpoints	"Time from start of first Treatment Cycle to qualification for re-treatment, as assessed by monitoring the total MG-ADL score (compared to TC_1B), in the active versus placebo group in the AChR-Ab seropositive patients." changed to "Time from TC_1V5 to qualification for re-treatment, as assessed by monitoring the total MG-ADL score (compared to TC_1B), in the active versus placebo group in the AChR-Ab seropositive patients."	A treatment period consists of 4 doses. It's only after these 4 doses that one could consider potential re-treatment and not from the first dose onwards. This is reflected in the updated endpoint. The endpoint is based on the MG-ADL criteria that allow for re-treatment and doesn't include other criteria that need to be fulfilled to allow re-treatment within this protocol.
SYNOPSIS Statistical Methods and Plan 8.4.2. Secondary Endpoint Analyses	"Time from start of first Treatment Cycle to qualification for re-treatment monitored by total MG-ADL score in AChR-Ab seropositive patients" changed to "Time from start of TC_1V5 to qualification for re-treatment monitored by total MG-ADL score in AChR-Ab seropositive patients if:	

Section	Change	Rationale
	- the patients has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms, and - no clinically meaningful improvement (decrease in total MG-ADL score from TC_1B < 2)."	
SYNOPSIS Trial Duration	"The trial duration is 26 weeks preceded by a Screening period of maximum 2 weeks." changed to 'The trial duration is 26 weeks preceded by a Screening period of approximately 2 weeks.'	In some cases, the screening period can be extended with up to 5 days
SYNOPSIS Methodology: TREATMENT CYCLES AND BASELINES 4.1 Summary of Trial Design	"The trial will include a Screening period (pre-randomization) of maximum 2 weeks, …" changed to "The trial will include a Screening period (pre-randomization) of approximately 2 weeks, …"	
Table 1 General Schedule of Assessments	Footnote d: "Randomization (at the first Treatment Cycle Baseline [TC_1B] only) should be performed as soon as possible after Screening with a maximum of 2 weeks, however only after confirmation of eligibility of the patient." changed to "Randomization (at the first Treatment Cycle Baseline [TC_1B] only) should be performed as soon as possible after Screening with approximately 2 weeks, however only after confirmation of eligibility of the patient."	

Section	Change	Rationale
SYNOPSIS ROLL-OVER	"Patients who discontinue early from randomized treatment for rescue or pregnancy reasons or for a (serious) adverse event ([S]AE) that might jeopardize the safety of the patient will also not be offered the option to roll over to the follow-on trial." changed to "Patients who discontinue 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 will also not be offered the option to roll over to the follow-on trial."	Change of wording to clarify that there needs to be a serious safety risk in order to have the patient discontinued.
4.4.2. Early Discontinuation from Randomized 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."	
4.1. Summary of Trial Design 4.5. Roll-Over to Follow-on Trial	"Patients who discontinue early from randomized treatment for rescue or pregnancy reasons or for an (S)AE that might jeopardize the safety of the patient will also not be offered the option to roll over to the follow-on trial." changed to "Patients who discontinue 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 will also not be offered the option to roll over to the follow-on trial."	

Section	Change	Rationale
5.2. Screening	"• Sampling to determine the AChR/MuSK-Ab serotype (seronegative or seropositive) of the patient. In case the AChR-Ab result is not available in time (within the 2 weeks screening window), the value found in the Medical History of the patient will be used for randomization." changed to "• Sampling to determine the AChR/MuSK-Ab serotype (seronegative or seropositive) of the patient. In case the AChR-Ab result is not available in time (i.e. within the 2 weeks screening window), the screening window can be enlarged on an ad-hoc base with maximum 5 calendar days."	The AChR-Ab medical history value will not be used anymore. Enlarging the screening window should allow sufficient time for the result to be provided by the central laboratory. This to maximize our consistency in our testing methods and results throughout the trial.
5.3. Randomization	"Randomization should be performed as soon as possible after Screening with a maximum of 2 weeks, however …" changed to "Randomization should be performed as soon as possible after Screening in approximately 2 weeks with a possible ad-hoc extension of maximum 5 calendar days in case of non-availability of AchR AB status, however …"	
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 post-infusion of IMP."	For patient safety, allowing for vaccines to be administered according to common clinical practice. Also to reduce the risk of confusing vaccination-related adverse adverse events (such as fever) with IMP-infusion related adverse events
6.8.1. Prohibited Medications during the Trial	"Vaccines" changed to "Live/live-attenuated vaccines"	

Section	Change	Rationale
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.
Appendix 6 Laboratory Evaluations Footer	"[2] In case the AChR-Ab result is not available in time (within the 2 weeks screening window), the value found in the Medical History of the patient will be used for randomization." changed to "[2] In case the AChR-Ab result is not available in time (i.e. within the 2 weeks screening window), the screening window can be enlarged on an ad-hoc base with maximum 5 calendar days.	The AChR-Ab medical history value will not be used anymore. Enlarging the screening window should allow sufficient time for the result to be provided by the central laboratory. This to maximize our consistency in our testing methods and results throughout the trial.

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
SYNOPSIS SAMPLE SIZE AND STRATIFICATION 4.1. Summary of Trial Design SAMPLE SIZE AND STRATIFICATION 6.5. Method of Assigning Patients to Treatment Group	"ethnicity" was removed and "patients" was added after "non-Japanese". The definition of "Japanese patient" was added.	"Japanese" is a race and not an ethnicity. Definition of "Japanese patient" added for completeness.
SYNOPSIS STANDARD of CARE (SoC) 4.1. Summary of Trial Design STANDARD of CARE (SoC)	Addition of the following sentences: "In case these medications are taken for another indication than MG, same conditions apply." "Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC."	Sentences added for extra clarification.
SYNOPSIS RE-TREATMENT 4.1. Summary of Trial Design RE-TREATMENT	"Each patient may start …" changed to "Each patient will start …"	Language changed to clarify that according to the study design, in this situation, the patient will get re-treatment (it is not a free choice).
	The first bullet has been changed from "The patient has completed the previous Treatment Cycle (including the assessments of the corresponding Visit 9) AND" to "The patient has completed the previous Treatment Cycle (i.e. an 8-week time period after first dosing date) AND"	Wording adjusted to cover the situation where Visit 9 would be missing.
SYNOPSIS RE-TREATMENT 4.1. Summary of Trial Design RE-TREATMENT	Addition of the following sentence: "Re-treatment with IMP may be reconsidered at next time where conditions for re-treatment are met, providing that at least 4 weeks have past after other MG treatment (see Appendix 9)"	Wording and appendix added for clarification.

Section	Change	Rationale
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), …" - "In situations where rescue therapy is given, patients will be discontinued early from randomized 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 randomized treatment."	Wording adjusted to enhance clarification.
SYNOPSIS Inclusion Criteria 4.3.1 Inclusion Criteria	Criterion no. 5: "*Note: AChE inhibitors must be held for at least …*" changed to "*Note: AChE inhibitors must be halted for at least …*"	Administrative change
SYNOPSIS Exclusion Criteria 4.3.2 Exclusion Criteria	Criterion no. 7: "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 Statistical Methods and Plan 8.4.1. Primary Endpoint Analyses	"ethnicity" was replaced twice with "Japanese/non-Japanese patient, AChR-Ab".	Administrative changes (added for completeness).

Section	Change	Rationale
Table 1 General Schedule of Assessments	Trial Day (Visit Window).	Visit window corrected.
	Changes to the table footer: - "[k] Samples for clinical laboratory tests (hematology and clinical chemistry)" changed to "[k] Samples for clinical laboratory tests (hematology, clinical chemistry and FSH, if applicable)" - "[q] Samples for anti-drug antibodies (ADAs) will be collected pre-dose on dosing days. As from … of the corresponding Treatment Cycle." changed to "[q] Samples for anti-drug antibodies (ADAs) will be collected pre-dose if sampling is to be performed on dosing days. During the first Treatment Cycle, samples for ADA will be taken at Visits 1, 4, 6 and 9. As from … of the corresponding Treatment Cycle and EoS/ED." - "[r] Pharmacokinetic (PK) samples will be collected at Visits 1, 2, 3, 4, 5, and 6." changed to "[r] Pharmacokinetic (PK) samples will be collected at Visits 1, 2, 3, 4, 5, and 6 and EoS/ED." - "[u] During the UNS visit, additional assessments can be performed at …" changed to "[u] During the UNS visit, additional assessments as indicated in the SoA can be performed at …"	Administrative changes.
LIST OF APPENDICES	Appendix 8 and Appendix 9 were added	For completeness.
LIST OF ABBREVIATIONS	C_{max} "Maximum observed plasma concentration" changed to "Maximum observed serum concentration"	Correction

Section	Change	Rationale
4.6. Protocol Deviations	"prior review and documented approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of an amendment, except …" changed to "prior review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Regulatory Authority as per local regulation, except …"	Administrative change
4.9. End of Trial Definition	The following was added: "4.9. End of Trial Definition End of trial is defined as last patient last visit."	Added for completeness (was missing in the previous version).
5.2. Screening	12th bullet: "Sampling to determine the AChR/MuSK-Ab serotype (seronegative or seropositive) of the patient." changed to "Sampling to determine the AChR/MuSK-Ab serotype (seronegative or seropositive) of the patient. In case the AChR-Ab result is not available in time (within the 2 weeks screening window), the value found in the Medical History of the patient will be used for randomization. "	To avoid missing information on stratification factor (at time of randomization) in case of late lab results
5.3. Randomization	Last paragraph: "…3 stratification factors: ethnicity (Japanese vs. non-Japanese), AChR-Ab status …" changed to "…3 stratification factors: Japanese vs. non-Japanese patients, AChR-Ab status …"	"Japanese" is a race and not an ethnicity.
	"… recorded as a screen failure in the IRT." changed to "… recorded as a screen failure in the EDC system."	Correction.

Section	Change	Rationale
6.8.1. Prohibited Medications	- "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 randomized treatment:" - "Rescue therapy" changed to "Rescue therapy when used in patients who meet the criteria to be rescued" - Additional bullet: "Use of PLEX or immunoadsorption more than once during study period"	Wording added for clarification.
6.8.2. Rescue Therapy	- First sentence ("If necessary, patients may receive rescue therapy if their gMG deteriorates.") deleted. - The following sentence added at the end of the section: "In situations where the treatments as listed above are given under the protocol defined rescue criteria, patients will be discontinued early from randomized treatment." - Last sentence ("In situations where rescue therapy is given, patients will be discontinued early from randomized treatment.") deleted.	To be in line with the corresponding section in the Synopsis, Section 4.1, and Section 6.8.1.
6.11. Handling Missed Doses in the 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 3days, …"	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.

Section	Change	Rationale
7.1.3. Myasthenia Gravis Composite	First sentence: "The MGC has 10 items (Appendix 3) combining physician examination and patient reported outcomes." changed to "The MGC has 10 items (Appendix 3) combining a trained rater's examination and patient reported outcomes."	Updated because the rater needs to be a trained person, but not necessarily a physician.
7.2.1.3. 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 3 deleted	Table deleted and text updated to clarify that all SAEs are to be followed-up until resolution.
7.2.1.4.1 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.
7.3. Pharmacokinetics	"(PK)" was added to the section title.	Added for completeness.
7.4. Pharmacodynamics	"(PD)" was added to the section title.	Added for completeness.
7.5. Anti-Drug Antibodies	"(ADA)" was added to the section title.	Added for completeness.
	Second sentence: "At Baseline (SEB and TC_nB), confirmatory and titer analysis will be performed using a validated ADA assay." changed to "At Baseline (SEB and TC_nB), Screening, confirmatory and titer analysis will be performed using a validated ADA assay."	Added for completeness (3-step analysis).
8.4.3. Tertiairy Endpoint Analyses	- Last paragraph: "…using individual concentration data in plasma and actual sampling times:" changed to "…using individual concentration data in serum and actual sampling times:" - "C_{max}: maximum observed plasma concentration" changed to "C_{max}: maximum observed serum concentration"	Correction (ARGX-113 is to be measured in serum and not in plasma).

Section	Change	Rationale
8.4.3. Tertiairy Endpoint Analyses	- "C_{trough}: plasma concentration observed pre-dose at Visits 2, 3 and 4" changed to "C_{trough}: serum concentration observed pre-dose at Visits 2, 3 and 4"	
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 (records and documents pertaining to the conduct of this trial and the distribution of IMP, including regulatory documents, eCRFs, signed patient ICFs, laboratory test results, IMP inventory records, source documents, …" - Third paragraph ("The United States (US) Food and Drug Administration (FDA) regulations … the Principal Investigator of these events.") deleted. - The following sentence was added to the end of the first paragraph: "The Sponsor will notify the Principal Investigator of these events."	Updated to avoid duplication of information.
Appendix 6 Laboratory Evaluations Clinical Chemistry AChR-/MuSK-antibody serotype Footer	- "*" changed to "1" - "[2]" was added to the end of the description. - "*" changed to "1" - "[2] In case the AChR-Ab result is not available in time (within the 2 weeks screening window), the value found in the Medical History of the patient will be used for randomization." was added.	Updated for extra clarification.
CCI [redacted]		

Section	Change	Rationale
Appendix 8 Decision Tree for Re-treatment – Part A	Figure and footnote added.	Added for completeness
Appendix 9 Decision Tree for Re-treatment – Part B	Figure and footnote added.	Added for completeness

SYNOPSIS

Name of Sponsor:	**argenx BVBA**	
Name of Investigational Medicinal Product (IMP):	**ARGX-113 (efgartigimod)**	
Name of Active Ingredient:	A human anti-neonatal Fc- receptor (FcRn) immunoglobulin G1 (IgG1) Fc fragment	
Indication:	Treatment of patients with generalized myasthenia gravis (gMG)	
Title of Trial:	A randomized, double-blind, placebo-controlled, multicenter Phase 3 trial to evaluate the efficacy, safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalized muscle weakness	
Protocol No:	ARGX-113-1704 (ADAPT)	
Trial Sites:	This trial is a global, multicenter trial	
Trial Duration: The trial duration is 26 weeks preceded by a Screening period of maximum approximately 2 weeks.		Phase: 3

Objectives:

Primary Objective:

- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "Myasthenia Gravis Activities of Daily Living (MG-ADL) responders" after the first Treatment Cycle in the acetylcholine receptor (AChR)-antibody (Ab) seropositive population.

Secondary Objectives:

- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "Quantitative Myasthenia Gravis (QMG) responders" after the first Treatment Cycle in the AChR-Ab seropositive population.
- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "MG-ADL responders" after the first Treatment Cycle in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- To evaluate the efficacy of ARGX-113 as assessed by the percentage of time that patients show a "clinically meaningful improvement" in total MG-ADL score during the trial (up to and including Day 126) in the AChR-Ab seropositive population.
- To evaluate the efficacy of ARGX-113 as assessed by the time to qualification for first re-treatment in the AChR-Ab seropositive population.
- To evaluate the onset of efficacy of ARGX-113 as assessed by the percentage of "early MG-ADL responders" after the first Treatment Cycle in the AChR-Ab seropositive population.
- To evaluate the safety and tolerability of ARGX-113 in the overall population and in subgroups.

Tertiary Objective:

- To assess additional efficacy and safety parameters, pharmacodynamics (PD) and immunogenicity.

Definitions

An "MG-ADL responder" is defined as a patient who shows a decrease of at least 2 points on the total MG-ADL score (compared to the corresponding Treatment Cycle Baseline [TCB]) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of IMP of the corresponding cycle. The scoring of MG-ADL should be performed by a trained and certified evaluator.

A "QMG responder" is defined as a patient who shows a decrease of at least 3 points on the total QMG score (compared to the corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of IMP of the corresponding cycle. The scoring of QMG should be performed by a trained evaluator.

An "early MG-ADL responder" is defined as a patient who shows a decrease of at least 2 points on the total MG-ADL score (compared to the corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring after 1 or maximum 2 infusions of IMP of the corresponding cycle. The scoring of MG-ADL should be performed by a trained and certified evaluator.

An MG-ADL "clinically meaningful improvement" is defined as a decrease of at least 2 points on the total MG-ADL score compared to either Study Entry Baseline (SEB) or corresponding TCB.

A QMG "clinically meaningful improvement" is defined as a decrease of at least 3 points on the total QMG score compared to either SEB or corresponding TCB.

Methodology:

DESCRIPTION

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial to evaluate the efficacy, safety, tolerability, quality of life and impact on normal daily activities of ARGX-113 in patients with gMG-.

The trial duration is 26 weeks, which consists of:

- a treatment part where all randomized patients will be treated with IMP, and
- a re-treatment part where patients may be re-treated with IMP on an "as needed basis" during the timeframe of the trial.

The trial will include patients on a stable standard of care (SoC) with a total MG-ADL score of ≥ 5 points at Screening and Baseline and with more than 50% of the total score attributed to non-ocular symptoms.

The time between Treatment Cycles is based on the duration of the treatment effect and may vary from patient to patient and within each patient from cycle to cycle (patient-tailored approach).

SAMPLE SIZE AND STRATIFICATION

Approximately 150 patients will be stratified according to 3 stratification factors:

Japanese vs. non-Japanese patients, AChR-Ab status (seropositive vs. seronegative) and SoC (patients on non-steroidal immunosuppressive drugs [NSIDs] vs. patients not on NSIDs) and randomized (1:1) within each stratum to be treated with either placebo or ARGX-113, on top of their current SoC. A maximum of 20% of AChR-Ab seronegative patients will be allowed in the trial.

Definition: Japanese patient is defined as a patient whose parents and four grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of > 10 years and currently lives in Japan.

TREATMENT CYCLES AND BASELINES

The trial will include a Screening period (pre-randomization) of approximately 2 weeks, a first Treatment Cycle and a variable number of subsequent Treatment Cycles administered on an "as needed basis". Each Treatment Cycle consists of 9 weekly visits over a period of 8 weeks, consisting of a Treatment period of 3

weeks (4 weekly infusions) and a Follow-up (FU) period of 5 weeks (see Figure 1). The SEB and the (first) Treatment

Cycle Baseline ($TC_{[1]}B$) will both be set at randomization (Visit 1), whilst the Baseline of each subsequent Treatment Cycle (TC_nB) will be set at Visit 1 of each corresponding Treatment Cycle.

SCREENING AND TREATMENT

During the Screening period, patient's eligibility for trial participation will be evaluated.

During the Treatment Cycles, eligible patients will receive, on top of their current SoC and in a blinded fashion, 4 weekly infusions of either 10 mg/kg ARGX-113 or placebo at Visit 1, Visit 2, Visit 3 and Visit 4 of the corresponding Treatment Cycle.

STANDARD of CARE (SoC)

Patients should be on a stable dose and frequency of SoC prior to Screening (inclusion criterion n°5). 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. In case these medications are taken for another indication than MG, same conditions apply.

For the entire duration of the trial, a change in the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed. 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.

TIME BETWEEN TREATMENT CYCLES

At the end of each Treatment Cycle, patients will enter a variable Inter Treatment Cycle (ITC) period during which they will be treated with their SoC only. The length of the ITC period may vary from patient to patient and for each patient from cycle to cycle (patient-tailored approach). The visit frequency in the ITC period is every two weeks, starting 14 days (± 2 days) from the last visit of the previous Treatment Cycle.

RE-TREATMENT

Each patient will start a new Treatment Cycle with ARGX-113 or placebo when all the following criteria apply:

- The patient has completed the previous Treatment Cycle (i.e. an 8-week time period after first dosing date) AND
- The patient has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms AND
- The Treatment Cycle can start at the latest on Day 127 and can be completed within the timeframe of the trial (26 weeks) AND
- In case the patient was an MG-ADL responder at the previous Treatment Cycle: if he/she has lost the response.
  Loss of response is defined as a patient who no longer shows a decrease of at least 2 points on the total MG-ADL score compared to the corresponding TCB.

However, patients may not receive re-treatment with ARGX-113 or placebo if, at the time of re-treatment, patients 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.

Re-treatment with IMP may be re-considered at next time where conditions for re-treatment are met, providing that at least 4 weeks have past after other MG treatment (see Appendix 9).

ROLL-OVER

At the End of Study (EoS) visit, patients will be offered the option to roll over into a long-term, single-arm, open-label follow-on trial (ARGX-113-1705) where they will be treated with ARGX-113 (10 mg/kg of body weight) on an "as needed basis".

Patients who need re-treatment but cannot complete a Treatment Cycle within the time frame of the ARGX-113-1704 trial (i.e., require re-treatment after Day 127), may roll over immediately to the follow-on trial to receive treatment with ARGX-113.

Patients who discontinue early from trial ARGX-113-1704, will not be offered the option to roll over in the follow-on trial.

Patients who discontinue 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 will also not be offered the option to roll over to the follow-on trial. Patients who discontinue early from randomized treatment for other reasons and patients who have a temporary interruption from randomized treatment may be offered the option to roll over to the follow-on trial.

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. 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 one 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 randomized treatment.

EARLY DISCONTINUATION FROM THE TRIAL

Any patient prematurely discontinuing the trial should perform the EoS/ED assessments.

EARLY DISCONTINUATION FROM RANDOMIZED TREATMENT

Patients who discontinue early from randomized treatment within a Treatment Cycle will have to complete the End of Treatment (EoT) assessments and complete the remaining visits in the current Treatment Cycle, according to the general schedule of assessments (SoA) (Table 1). These patients will not receive any further IMP administration during the trial and will continue to be followed for safety and disease severity (limited to MG-ADL and QMG) as per the SoA for Patients that Discontinued Early from Randomized Treatment (Table 2).

Patients who discontinue early from randomized treatment in the ITC period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per Table 2.

TEMPORARY INTERRUPTION FROM RANDOMIZED TREATMENT

A patient that does not need to be discontinued early from randomized treatment might still have a temporary interruption from randomized treatment which is defined as a discontinuation only from the current Treatment

Cycle. Therefore, these patients might still be eligible for further additional treatments with IMP within this trial.	
Planned Number of Patients:	Approximately 150 patients will be randomized.
Criteria for Inclusion and Exclusion:	Inclusion Criteria: 1. Patients with the ability to understand the requirements of the trial, provide written informed consent, and comply with the trial protocol procedures. 2. Male or female patients aged ≥ 18 years. 3. Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) class II, III, IVa and IVb. The confirmation of the diagnosis should be documented and supported by at least 1 of the following 3 tests: o History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation, or o History of positive edrophonium chloride test, or o Patient has demonstrated improvement in MG signs on oral AChE inhibitors as assessed by the treating physician. 4. A total MG-ADL score of ≥ 5 points at Screening and Baseline (SEB) with more than 50% of the total score due to non-ocular symptoms. 5. Patients are required to be on a stable dose of their MG treatment (SoC) prior to Screening. The SoC is limited to AChE inhibitors, steroids and NSIDs. For patients receiving NSIDs, steroids, and/or AChE inhibitors as concomitant medications the following stability dose conditions will apply: o Non-steroidal immunosuppressive drugs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months prior to Screening and no dose changes in the last 3 months before Screening. o Steroids: treatment initiated at least 3 months prior to Screening and no dose changes in the last month before Screening. o Acetylcholinesterase inhibitors: stable dose with no dose escalation in the past 2 weeks before Screening. *Note: AChE inhibitors must be halted for at least 12 hours consistent with the revised manual for the QMG test as recommended by the MGFA, before the QMG assessment*.
	Exclusion Criteria: 1. 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 (see DEFINITION OF TERMS) should have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (SEB) prior to administration of IMP.

	Note: Women of childbearing potential should use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month, of combined estrogen and progestogen hormonal contraception with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or agree upon continuous abstinence from heterosexual sexual contact. 2. 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. *Note: Sterilized male patients who have had vasectomy with documented aspermia post-procedure, or male patients who have a partner of non-childbearing potential, can be included.* 3. MGFA Class I and V patients. 4. Patients with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, fluoroquinolones, beta-blockers, etc.). 5. Patients with known seropositivity or who test positive for an active viral infection at Screening with: o Hepatitis B Virus (HBV) (except patients who are seropositive because of HBV vaccination) o Hepatitis C Virus (HCV) o Human Immunodeficiency Virus (HIV) 6. Patients with any known severe bacterial, viral or fungal infection or any major episode of infection that required hospitalization or injectable antimicrobial therapy in the last 8 weeks prior to Screening. 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 total IgG level < 6 g/L at Screening. 9. Patients with documentation of a lack of clinical response to PLEX. 10. Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to Screening. 11. Immunoglobulins given by IV (IVIg), subcutaneous or intramuscular route, or PLEX, each within 1 month prior to Screening. 12. Patients who have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders, unless deemed cured by adequate treatment with no evidence of recurrence for ≥ 3 years before Screening. Patients with completely excised non-melanoma skin cancer (such as basal cell carcinoma or

	squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time. 13. Thymectomy when performed < 3 months prior to Screening or planned to be performed during the trial period. 14. Patients with clinical evidence of other significant serious 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. 15. Patients who previously participated in a clinical trial with ARGX-113. 16. Patients who received a vaccination (e.g., influenza vaccine) within the last 4 weeks prior to Screening. 17. Use of any monoclonal antibody, such as rituximab and eculizumab, within 6 months prior to first dosing.
Test Product, Dose and Mode of Administration:	In this trial, the test product is ARGX-113, which is a human anti-neonatal Fc receptor IgG1 Fc fragment. At Visits 1, 2, 3 and 4 of each Treatment Cycle, a dose of 10 mg/kg of body weight of ARGX-113 will be administered as an intravenous (IV) infusion over a period of 1 hour. The total dose per IMP infusion is capped at 1200 mg for patients with body weight ≥ 120 kg.
Placebo, Dose, and Mode of Administration:	Matching placebo with same buffer components as the test product, but without the active substance will be administered as an IV infusion over a period of 1 hour at Visits 1, 2, 3 and 4 of each Treatment Cycle.

Criteria for Evaluation:

Primary Endpoint:

- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.

Secondary Endpoints:

- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 3 points on the total QMG score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.
- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Percentage of time that patients have a "clinically meaningful improvement" in total MG-ADL score compared to SEB during the trial (up to and including Day 126) in the active versus placebo group in AChR-Ab seropositive patients.
- Time from TC_1V5 to qualification for re-treatment, as assessed by monitoring the total MG-ADL score (compared to TC_1B), in the active versus placebo group in the AChR-Ab seropositive patients.
- Percentage of patients who, after the first Treatment Cycle, show a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest after 1 or maximum 2 infusions of the IMP in the active versus the placebo group in AChR-Ab seropositive patients.

Tertiary Endpoints:

- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.
- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 3 points on the total QMG score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.
- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of the IMP in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Percentage of time that patients have a "clinically meaningful improvement" in total MG-ADL score compared to SEB during the trial (up to and including Day 126) in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Total 15 item Quality of life scale for Myasthenia Gravis [revised version] (MG-QoL15r) score change from Baseline - SEB and TC_nB (Visit 1) - to each time point in the active and placebo group.

Statistical Methods and Plan

The null hypothesis H0 states that there is no difference in proportion of MG-ADL responders between patients treated with placebo and ARGX-113. The trial is powered at 90% using significance level of 5% 2-sided to test the alternative hypothesis of that the difference in the proportion of responders is 29% in favor of patients treated with ARGX-113. The proportion MG-ADL responders amongst patients treated with placebo is hypothesized to be 30%. In order to test this alternative hypothesis, a sample size of 150 patients is needed, with this allowing for 10% attrition rate.

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.

The efficacy endpoints will be tested in the modified Intention-To-Treat (mITT) and the Per Protocol (PP) populations. The primary endpoint is tested by means of a 2-sided exact test (using logistic regression) stratified for the stratification factors Japanese/non-Japanese patient, AChR-Ab serotype and SoC at the 2-sided 5% significance level, in the AChR-Ab seropositive patients. Percentage responders will be compared between ARGX-113 and placebo using logistic regression model with Baseline total score as covariate and Japanese/non-Japanese patient, AChR-Ab serotype and SoC as stratification variables.

The set of primary and secondary efficacy hypotheses will be tested using hierarchical testing principle at 5% significance level in the following order:

1. MG-ADL responders after the first Treatment Cycle in AChR-Ab seropositive patients
2. QMG responders after the first Treatment Cycle in AChR-Ab seropositive patients
3. MG-ADL responders after the first Treatment Cycle in overall population (AChR-Ab seropositive and AChR-Ab seronegative patients)
4. Percentage of time patients have a "clinically meaningful improvement" in total MG-ADL score in AChR-Ab seropositive patients
5. Time from TC_1V5 to qualification for re-treatment monitored by total MG-ADL score in AChR-Ab seropositive patients if:
   - the patients has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms, and
   - no clinically meaningful improvement (decrease in total MG-ADL score from $TC_1B < 2$).
6. Early MG-ADL responders after the first Treatment Cycle in AChR-Ab seropositive patients

The secondary endpoints “QMG responders after the first Treatment Cycle in AChR-Ab seropositive patients, MG-ADL responders after the first Treatment Cycle in the overall population, and early MG-ADL responders after the first Treatment Cycle in AChR-Ab seropositive patients” will be analyzed using the same methodology as for the primary endpoint. The secondary endpoint “Percentage of time patients have a clinically meaningful improvement in total MG-ADL score in AChR-Ab seropositive patients” will be analyzed using an analysis of covariance (ANCOVA) model with terms for randomized treatment and Baseline total MG-ADL score as a covariate; the model will be stratified for the stratification variables. The secondary endpoint “Time from TC_1V5 to qualification for re-treatment monitored by total MG-ADL score in AChR-Ab seropositive patients” will be analyzed using Kaplan-Meier time to event analysis (stratified log-rank test), stratified for the stratification variables.

The continuous endpoints, i.e., total score changes from Baseline, between treatment groups at a specific day post-Baseline (SEB and TCnB), will be analyzed by means of Mixed Models for Repeated Measurements (MMRM). Baseline total score values will be included in the MMRM as well as the stratification factors. Moreover, summary statistics will be provided for all continuous endpoints.

Frequency tables will be made for all binary variables, including AEs.

Table 1 General Schedule of Assessments

Assessment	Screening	Treatment Period				Follow-up (FU) Period					ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1V2	TC_1V3	TC_1V4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9			
Trial Day (Visit Window)	Day -14 to -1	1	8±1	15±1	22±1	29±1	36±1	43±1	50±1	57±1	ITC_nVn	EoS/ED	UNS[u]
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_nB)	TC_nV2	TC_nV3	TC_nV4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+7) ±1	(X+14) ±1	(X+21) ±1	(X+28) ±1	(X+35) ±1	(X+42) ±1	(X+49) ±1	(X+56) ±1	Y±2	182±3	
					EoT[v]								
Informed consent[c]	X												
Inclusion/exclusion criteria	X	X											
Medical/surgical history	X												
Demographic characteristics	X												
Randomization[d]		X											
MG-ADL[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
QMG[e]		X	X	X	X	X	X	X	X	X	X	X	X
MGC[e]		X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[e]		X	X	X	X	X	X	X	X	X	X	X	X
MG-QoL15r[e]		X	X	X	X	X	X	X	X	X	X	X	X
Suicidality assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[h]	X											X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
AChR-/MuSK-antibody serotype	X												
Urinalysis[l]	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Screening	Treatment Period				Follow-up (FU) Period					ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1V2	TC_1V3	TC_1V4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9			
Trial Day (Visit Window)	Day -14 to -1	1	8±1	15±1	22±1	29±1	36±1	43±1	50±1	57±1	ITC_nVn	EoS/ED	UNS[u]
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_nB)	TC_nV2	TC_nV3	TC_nV4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+7) ±1	(X+14) ±1	(X+21) ±1	(X+28) ±1	(X+35) ±1	(X+42) ±1	(X+49) ±1	(X+56) ±1	Y±2	182±3	
					EoT[v]								
Serum pregnancy test[m]	X												
Urine pregnancy test[n]		X	X	X	X	X	X	X	X	X	X	X	X
Anti-AChR/anti-MuSK antibodies[o]		X	X	X	X	X	X	X	X	X	X	X	X
Total IgG and its subtypes[o]		X	X	X	X	X	X	X	X	X	X	X	X
Viral tests[p]	X												
ADA[q]		X			X[q]		X[q]			X		X	X
Pharmacokinetics[r]		X	X	X	X	X	X					X	X
Administration of ARGX-113 or placebo[s]		X[t]	X	X	X								
Prior[w]/concomitant/ rescue therapy	<---------- X ---------->												
Adverse events	<---------- X ---------->												

AChR = Acetylcholine Receptor; ADA = Anti-Drug Antibodies; ECG = Electrocardiogram; ED = Early Discontinuation; EoS = End of Study; EoT = End of Treatment; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels; IgG = Immunoglobulin G; ITC(V) = Inter Treatment Cycle (Visit); MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QoL15r = 15-item Quality of Life scale for Myasthenia Gravis [Revised version]; MuSK: Muscle-Specific Kinase; QMG = Quantitative Myasthenia Gravis; SCR = Screening; SEB = Study Entry Baseline; TCB = Treatment Cycle Baseline; TCV = Treatment Cycle Visit; UNS = Unscheduled; V = Visit.

[a] The Inter Treatment Cycle (ITC) period consists of visits every 2 weeks, starting 14 days (± 2 days) from the last visit of the previous Treatment Cycle. The visit denominator ('n') will start at 1 at each period. At each ITC_nV, an evaluation of the need for re-treatment should be done prior to decide whether assessments listed for ITC_nV or TC_nV1 are to be performed.

[b] Last Treatment Cycle in the trial should not start later than on Day 127 of the trial. If the patient is in need of re-treatment after this date, the patient should have the EoS/ED visit performed and, if eligible, he/she can roll-over into the long-term, single-arm, open-label follow-on ARGX-113-1705 trial.

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

[d] Randomization (at the first Treatment Cycle Baseline [TC_1B] only) should be performed as soon as possible after Screening with approximately 2 weeks, however only after confirmation of eligibility of the patient.

[e] Efficacy and quality of life assessments should be completed pre-dose on each dosing day and should be performed prior to any other trial-specific assessment, except for obtaining informed consent at Screening and the weight assessment, if applicable. The MG-ADL scale needs to be performed prior to all other efficacy or quality of life assessments. Acetylcholinesterase (AChE) 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 Inc [MGFA]). A total MG-ADL score ≥ 5 with more than 50% of this total score attributed to non-ocular symptoms should be met at Screening and Baseline (TC_nB).

[f] Suicidal ideation and behavior will be assessed pre-dose on dosing days via a targeted question based on the Patient Health Questionnaire item 9 (PHQ-9) (Simon, Rutter et al. 2013).

[g] The physical examination will be performed pre-dose on dosing days. See Section 7.2.3 for an overview of the different assessments.

[h] Height will be measured at Screening only and weight will be measured at Screening, at the EoS/ED visit, and when there is an obvious weight change compared to the last weight assessment.

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

[j] ECG will be performed pre-dose on dosing days.

[k] Samples for clinical laboratory tests (hematology, clinical chemistry and FSH, if applicable) will be collected pre-dose on dosing days (see Appendix 6). In addition, total IgG at Screening is to be assessed for defining eligibility. Patients need to be fasted at least 8 hours prior to each sampling.

[l] Urine samples will be collected pre-dose on dosing days (see Appendix 6).

[m] A serum pregnancy test will be performed on the samples taken for clinical laboratory tests (only for women of childbearing potential, see DEFINITION OF TERMS).

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

[o] Samples for pharmacodynamic (PD) biomarkers will be collected pre-dose on dosing days (see Appendix 6). Anti-AChR antibodies will be measured in AChR-Ab seropositive patients only. Anti-MuSK antibodies will be measured in MuSK-Ab seropositive patients only.

[p] Viral tests will be performed on samples taken at Screening (see Appendix 6).

[q] Samples for anti-drug antibodies (ADAs) will be collected pre-dose if sampling is to be performed on dosing days. During the first Treatment Cycle, samples for ADA will be taken at Visits 1, 4, 6 and 9. As from the second Treatment Cycle onwards, samples for ADA will only be taken at Visits 1 and 9 of the corresponding Treatment Cycle and EoS/ED.

[r] Pharmacokinetic (PK) samples will be collected at Visits 1, 2, 3, 4, 5, and 6 and EoS/ED. On dosing days, PK samples will be collected pre-dose (within 1 hour prior to start of infusion) and after the end of each infusion (within 1 hour after end of infusion).

[s] The Investigational Medicinal Product (IMP; ARGX-113 or placebo) will be administered as an intravenous (IV) infusion over a period of 1 hour at Visits 1, 2, 3, and 4. 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.

[t] At TC_nV1, the conditions for re-treatment will be checked before administration of the IMP.

[u] An unscheduled (UNS) visit can be on 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.

[v] For patients who discontinue early from randomized treatment, the assessments will depend on the visit at which it was decided that the patient had to discontinue early from randomized treatment (see Section 5.6). Patients who discontinue early from randomized treatment within a Treatment Cycle will have to complete the EoT assessments and complete the remaining visits in the current Treatment Cycle prior to entering the Safety and Disease Severity Follow-up (FU) period as per the SoA for Patients who Discontinued Early from Randomized Treatment (Table 2). These patients will not receive any further IMP administration during the trial. Patients who discontinue early from randomized treatment in the ITC period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per Table 2.

[w] Clinically relevant prior treatment will only be recorded once at Screening.

Table 2 Schedule of Assessments for Patients who Discontinued Early from Randomized Treatment[a]

Assessment	Safety and Disease Severity Follow-up Period[b]	End of Study / Early Trial Discontinuation[c]	Unscheduled
Visit	**FU_n**	**EoS/ED**	**UNS[d]**
Trial Day (Visit Window)	**Z+30 to 182 (±3)**	**182±3**	
Disease severity assessment			
MG-ADL[e]	X	X	X
QMG[e]	X	X	X
Safety follow-up			
Urine pregnancy test[f]	X	X	X
Concomitant/rescue therapy	<----------X---------->		
Adverse events	<----------X---------->		

ED = Early Discontinuation; EoS = End of Study; EoT = End of Treatment; FU = Follow-up; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; UNS = Unscheduled; Z = last visit performed as per Table 1.

[a] This schedule of assessments (SoA) is to be followed for patients who discontinue early from randomized treatment. Patients who discontinue early from randomized treatment within a Treatment Cycle will have to complete the EoT assessments and complete the remaining visits in the current Treatment Cycle, prior to entering the Safety and Disease Severity Follow-up period as per this SoA. These patients will not receive any further IMP administration during the trial. Patients who discontinue early from randomized treatment in the Inter Treatment Cycle (ITC) period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period.

[b] After the patient completed either the current Treatment Cycle or the EoT assessments of the current ITC visit if decision was made in the ITC period, the patient should return every month for the Safety and Disease Severity Follow-up visits until Day 182 as per this SoA.

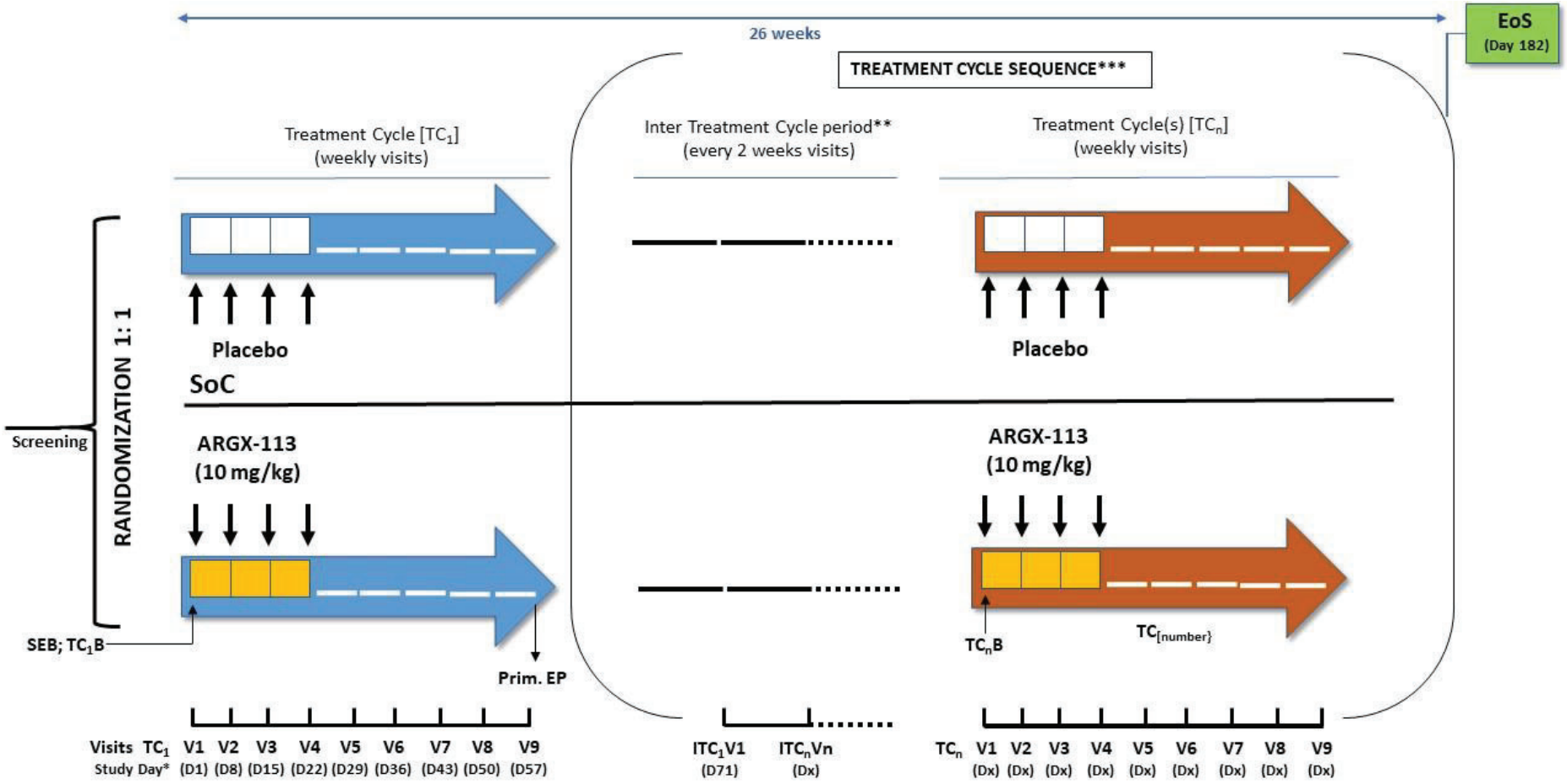
[c] For patients who discontinue early from randomized treatment, only a limited number of assessments need to be performed at the EoS/ED visit.

[d] An unscheduled (UNS) visit can be on request of the patient or the Investigator. During the UNS visit, additional assessments can be performed at the discretion of the Investigator, depending on the reason for the UNS visit.

[e] Disease severity assessments should be performed prior to any other trial-specific assessment in the following sequence: 1) MG-ADL, 2) QMG. 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 Inc [MGFA]).

[f] A urine pregnancy test will be performed only for women of childbearing potential (see DEFINITION OF TERMS).

Figure 1 Trial Design



** ± 1 day for Treatment Cycle visits and ± 2 days for Inter Treatment Cycle visits; ** Interval time may vary from patient to patient; *** May be repeated as many times as needed during the time frame of the trial. Last Treatment Cycle should not start later than on Day 127 of the trial.*
EoS = End of Study; Prim. EP = Primary Endpoint; ITC = Inter Treatment Cycle; SEB = Study Entry Baseline; SoC = Standard of Care; TC = Treatment Cycle; TC_nB = Treatment Cycle $_{[number]}$ Baseline

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Ab	Antibody
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
ANCOVA	Analysis of covariance
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed serum concentration
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
EDC	Electronic data capture
EoS	End of Study
EoT	End of Treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
Fc	Fragment, crystallized
FcRn	neonatal Fc Receptor
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FU	Follow-up
GCP	Good Clinical Practice
gMG	Generalized myasthenia gravis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product

IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITC	Inter treatment cycle
IV	Intravenous
IVIg	Intravenous immunoglobulin
LRP4	Lipoprotein receptor-related protein-4
LS	Least square means
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	15-item Quality of life scale for Myasthenia Gravis [revised version]
mITT	modified Intention-To-Treat
MMRM	Mixed Models for Repeated Measurements
MuSK	Muscle-specific kinase
NCI	National Cancer Institute
NSID	Non-steroidal immunosuppressive drug
PD	Pharmacodynamics
PHQ-9	Patient Health Questionnaire item 9
PLEX	Plasma Exchange
PK	Pharmacokinetics
PP	Per protocol
QMG	Quantitative Myasthenia Gravis
SAE	Serious adverse event
SEB	Study entry baseline
SoA	Schedule of assessments
SoC	Standard of care
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TCB	Treatment cycle baseline
TC_1B	First Treatment Cycle Baseline
TC_nB	Subsequent Treatment Cycle Baseline
TEAE	Treatment-emergent adverse event
UN	Unstructured covariance structure
UNS	Unscheduled visit
US	United States
WBC	White blood cell
WHO(-DD)	World Health Organization (drug dictionary)

DEFINITION OF TERMS

Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased trial outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a (serious) adverse event ([S]AE). In a double-blind trial, the subject, the Investigator and Sponsor staff who are involved in the treatment or clinical evaluation of the subjects and the review or analysis of data are all unaware of the treatment assignment.
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 (i.e., who had a hysterectomy, bilateral oophorectomy, or have current documented tubal ligation or any other permanent female sterilization procedure). 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.
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 the 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) one or more obligations of argenx BVBA, e.g., development of a protocol, selection and/or monitoring of Investigators, evaluation of reports, preparation of materials to be submitted to Health Authorities.
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 randomization into the trial based upon strict adherence to inclusion/exclusion criteria.
Good clinical practices (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. (International Council for Harmonization [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 Harmonization (ICH):	The International Conference on Harmonization 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 three regions to discuss scientific and technical aspects of pharmaceutical product registration.
Investigational medicinal product:	A pharmaceutical form of an active ingredient or placebo 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.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Treatment:	Term used throughout the clinical trial to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the trial randomization or treatment allocation.

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 (Howard, Barohn et al. 2013).

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 (Gilhus and Verschuuren 2015).

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 LPR4. All these autoantibodies belong to the immunoglobulin G (IgG) class (Gilhus and Verschuuren 2015; Gilhus 2016).

In approximately 5-20% of the MG patients, no serum antibodies against neuromuscular junction proteins can be detected (Vincent, Lang et al. 2006; Kaminski 2016). 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 (Gilhus 2016).

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 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 (Roopenian and Akilesh 2007; Challa, Velmurugan et al. 2014).

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

ARGX-113 is a human IgG1-derived Fc fragment of the za allotype that binds with nanomolar affinity to human FcRn. ARGX-113 encompasses IgG1 residues D220-K447 (EU numbering scheme) and has been modified with the so-called ABDEG™ technology (ABDEG™ = antibody that enhances IgG degradation) (Vaccaro, Zhou et al. 2005) to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of ARGX-113 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 ARGX-113, 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 ARGX-113 or a full-length mAb analogue (HEL-ABDEG™) (Patel, Puig-Canto et al. 2011; Challa, Bussmeyer et al. 2013).

The antibody clearing properties of ARGX-113 were confirmed in PK/PD studies in cynomolgus monkeys. A single infusion of ARGX-113 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 ARGX-113 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 ARGX-113 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 ARGX-113. The trial showed that a single administration of ARGX-113 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 ARGX-113. IV administration of ARGX-113 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 ARGX-113 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 ARGX-113 (10 mg/kg) or placebo in 4 infusions administered one week apart in addition to standard of care (SoC). The clinical effect of ARGX-113 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), Myasthenia Gravis Composite (MGC), and 15 item Quality of life scale for Myasthenia Gravis [revised version] (MG-QoL15r). 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 ARGX-113 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 the 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 in line 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 efficacy, safety and tolerability of ARGX-113 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 Harmonization, Good Clinical Practice (ICH GCP), Declaration of Helsinki, and other applicable regulatory requirements.

1.3. Standard of Care and Rationale for Use of ARGX-113

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

Acetylcholinesterase (AChE) inhibitors are frequently used in treatment of 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 the exposure of acetylcholine, which leads to an amelioration of the signs/symptoms of MG. Acetylcholinesterase inhibitors provide a symptomatic treatment of MG and do not act on the underlying pathogenic mechanism of the disease. Acetylcholinesterase inhibitors however do not work in all patients with MG and usually have a short duration of action requiring to be taken several times a day.

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. Non-steroidal immunosuppressive drugs 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 (Gilhus and Verschuuren 2015; Gilhus 2016).

Apart from the SoC described above, new biologic agents such as rituximab and eculizumab are also used in the treatment of 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 (Nowak, Dicapua et al. 2011; Howard, Utsugisawa et al. 2017).

Exacerbations of MG are treated using either therapeutic Plasma Exchange (PLEX), immunoadsorption or IVIg. In the case of PLEX, typically one exchange, removing one to two plasma volumes, is done every other day up to a total of four to six 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 (Meriggioli and Sanders 2009; Liu, Wang et al. 2010). 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 (Gilhus and Verschuuren 2015; Gilhus 2016).

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 (Drachman 1994; Gilhus and Verschuuren 2015; Gilhus 2016; Wolfe, Kaminski et al. 2016).

Following administration of ARGX-113 (10 mg/kg) in 4 infusions administered one 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 ARGX-113 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 ARGX-113 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. ARGX-113 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. ARGX-113 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 in line with the observed PD data, namely a reduction of total IgG and subtypes and a decreased level of AChR autoantibodies. Therefore, ARGX-113 is believed to be a promising treatment to reduce autoantibodies in gMG patients.

1.4. Benefit-Risk Assessment

Benefits

The clinical effect of ARGX-113 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 ARGX-113. 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). ARGX-113 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 ARGX-113 treatment over placebo. For all MG scales, a greater maximum mean change from Baseline (reduction) was observed in the ARGX-113 treatment group compared with placebo.

Risks

There have been no major safety findings arising from the ongoing and completed studies or any pattern of AEs which would raise concerns or alter the potential benefit-risk profile of ARGX-113.

Please refer to the current Investigator Brochure (IB), Section 5.5, for the summary of potential risks and benefits of ARGX-113.

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).

Taking into account the efficacy and safety data collected up to date and the design of the trial, which minimizes the risk to patients participating in this trial, the potential risks identified in association with ARGX-113 are justified by the potential benefits that may be afforded to patients receiving ARGX-113.

2. TRIAL OBJECTIVES

2.1. Primary Objective

- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "MG-ADL responders" after the first Treatment Cycle in the AChR-antibody (Ab) seropositive population.

2.2. Secondary Objectives

- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "QMG responders" after the first Treatment Cycle in the AChR-Ab seropositive population.
- To evaluate the efficacy of ARGX-113 as assessed by the percentage of "MG-ADL responders" after the first Treatment Cycle in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- To evaluate the efficacy of ARGX-113 as assessed by the percentage of time that patients show a "clinically meaningful improvement" in total MG-ADL score during the trial (up to and including Day 126) in the AChR-Ab seropositive population.
- To evaluate the efficacy of ARGX-113 as assessed by the time to qualification for first re-treatment in the AChR-Ab seropositive population.
- To evaluate the onset of efficacy of ARGX-113 as assessed by the percentage of "early MG-ADL responders" after the first Treatment Cycle in the AChR-Ab seropositive population.
- To evaluate the safety and tolerability of ARGX-113 in the overall population and in subgroups.

2.3. Tertiary Objective

- To assess additional efficacy and safety parameters, PD and immunogenicity.

Definitions

An "MG-ADL responder" is defined as a patient who shows a decrease of at least 2 points on the total MG-ADL score (compared to the corresponding Treatment Cycle Baseline [TCB]) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of IMP of the corresponding cycle. The scoring of MG-ADL should be performed by a trained and certified evaluator.

A "QMG responder" is defined as a patient who shows a decrease of at least 3 points on the total QMG score (compared to the corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of IMP of the corresponding cycle. The scoring of QMG should be performed by a trained evaluator.

An "early MG-ADL responder" is defined as a patient who shows a decrease of at least 2 points on the total MG-ADL score (compared to the corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring after 1 or maximum 2 infusions of IMP of the corresponding cycle. The scoring of MG-ADL should be performed by a trained and certified evaluator.

An MG-ADL "clinically meaningful improvement" is defined as a decrease of at least 2 points on the total MG-ADL score compared to either Study Entry Baseline (SEB) or corresponding TCB.

A QMG "clinically meaningful improvement" is defined as a decrease of at least 3 points on the total QMG score compared to either SEB or corresponding TCB.

3. TRIAL ENDPOINTS

3.1. Primary Endpoint

- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.

3.2. Secondary Endpoints

- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 3 points on the total QMG score (compared to TC_1B) for at least 4 consecutive weeks

with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.

- Percentage of patients who, after the first Treatment Cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Percentage of time that patients have a "clinically meaningful improvement" in total MG-ADL score compared to SEB during the trial (up to and including Day 126) in the active versus placebo group in AChR-Ab seropositive patients.
- Time from TC_1V5 to qualification for re-treatment, as assessed by monitoring the total MG-ADL score (compared to TC_1B), in the active versus placebo group in the AChR-Ab seropositive patients.
- Percentage of patients who, after the first Treatment Cycle, show a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest after 1 or maximum 2 infusions of the IMP in the active versus the placebo group in AChR-Ab seropositive patients.

3.3. Tertiary Endpoints

- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.
- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 3 points on the total QMG score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients.
- Percentage of patients who, from the second Treatment Cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding TCB) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of the IMP in the active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
- Percentage of time that patients have a "clinically meaningful improvement" in total MG-ADL score compared to SEB during the trial (up to and including Day 126) in the

active versus placebo group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

- Total MG-QoL15r score change from Baseline - SEB and TC_nB (Visit 1) - to each time point in the active and placebo group.

4. INVESTIGATIONAL PLAN

4.1. Summary of Trial Design

DESCRIPTION

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial to evaluate the efficacy, safety, tolerability, quality of life and impact on normal daily activities of ARGX-113 in patients with gMG.

The trial duration is 26 weeks, which consists of:

- a treatment part where all randomized patients will be treated with IMP, and
- a re-treatment part where patients may be re-treated with IMP on an "as needed basis" during the timeframe of the trial.

The trial will include patients on a stable SoC with a total MG-ADL score of ≥ 5 points at Screening and Baseline and with more than 50% of the total score attributed to non-ocular symptoms.

The time between Treatment Cycles is based on the duration of the treatment effect and may vary from patient to patient and for each patient from cycle to cycle (patient-tailored approach).

SAMPLE SIZE AND STRATIFICATION

Approximately 150 patients will be stratified according to 3 stratification factors: Japanese vs. non-Japanese patient, AChR-Ab status (seropositive vs. seronegative) and SoC (patients on NSIDs vs. patients not on NSIDs) and randomized (1:1) within each stratum to be treated with either placebo or ARGX-113, on top of their current SoC. A maximum of 20% of AChR-Ab seronegative patients will be allowed in the trial.

Definition: A Japanese patient is defined as a patient whose parents and four grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of > 10 years and currently lives in Japan.

TREATMENT CYCLES AND BASELINES

The trial will include a Screening period (pre-randomization) of approximately 2 weeks, a first Treatment Cycle and a variable number of subsequent Treatment Cycles administered on an "as needed basis". Each Treatment Cycle consists of 9 weekly visits over a period of

8 weeks, consisting of a Treatment period of 3 weeks (4 weekly infusions) and a Follow-up (FU) period of 5 weeks (see Figure 1). The SEB and the (first) Treatment Cycle Baseline ($TC_{[1]}B$) will both be set at randomization (Visit 1), whilst the Baseline of each subsequent Treatment Cycle (TC_nB) will be set at Visit 1 of each corresponding Treatment Cycle.

SCREENING AND TREATMENT

During the Screening period, patient's eligibility for trial participation will be evaluated.

During the Treatment Cycles, eligible patients will receive, on top of their current SoC and in a blinded fashion, 4 weekly infusions of either 10 mg/kg ARGX-113 or placebo at Visit 1, Visit 2, Visit 3 and Visit 4 of the corresponding Treatment Cycle.

STANDARD OF CARE (SoC)

Patients should be on a stable dose and frequency of SoC prior to Screening as detailed in Section 4.3.1 (inclusion criterion n°5). Permitted SoC for MG treatment under this protocol include NSIDs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as AChE inhibitors. In case these medications are taken for another indication than MG, same conditions apply.

For the entire duration of the trial, a change in the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed. Administration of AChE inhibitors must be halted for at least 12 hours prior to performing the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]) (Barohn 2000). Following this requirement, this possible temporary change in dosing regimen of AChE inhibitors will not be considered as a change in SoC.

TIME BETWEEN TREATMENT CYCLES

At the end of each Treatment Cycle, patients will enter a variable Inter Treatment Cycle (ITC) period during which they will be treated with their SoC only. The length of the ITC period may vary from patient to patient and for each patient from cycle to cycle (patient-tailored approach). The visit frequency in the ITC period is every two weeks, starting 14 days (± 2 days) from the last visit of the previous Treatment Cycle.

RE-TREATMENT

Each patient will start a new Treatment Cycle with ARGX-113 or placebo when all the following criteria apply (see Appendix 8):

- The patient has completed the previous Treatment Cycle (i.e. an 8-week time period after first dosing date) AND
- The patient has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms AND

- The Treatment Cycle can start at the latest on Day 127 and can be completed within the timeframe of the trial (26 weeks) AND
- In case the patient was an MG-ADL responder at the previous Treatment Cycle: if he/she has lost the response.

  Loss of response is defined as a patient who no longer shows a decrease of at least 2 points on the total MG-ADL score compared to the corresponding TCB.

However, patients may not receive re-treatment with ARGX-113 or placebo if, at the time of re-treatment, patients 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. Re-treatment with IMP may be reconsidered at next time where conditions for re-treatment are met, providing that at least 4 weeks have past after other MG treatment (see Appendix 9).

ROLL-OVER

At the EoS visit, patients will be offered the option to roll over into a long-term, single-arm, open-label follow-on trial (ARGX-113-1705) where they will be treated with ARGX-113 (10 mg/kg of body weight) on an "as needed basis".

Patients who need re-treatment but cannot complete a Treatment Cycle within the time frame of the ARGX-113-1704 trial (i.e., require re-treatment after Day 127), may roll over immediately to the follow-on trial to receive treatment with ARGX-113.

Patients who discontinue early from trial ARGX-113-1704, will not be offered the option to roll over in the follow-on trial.

Patients who discontinue 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 will also not be offered the option to roll over to the follow-on trial.

Patients who discontinue early from randomized treatment for other reasons and patients who have a temporary interruption from randomized treatment may be offered the option to roll over to the follow-on trial.

RESCUE THERAPY

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 one 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 randomized treatment (see Section 4.4.2).

EARLY DISCONTINUATION FROM THE TRIAL

Any patient prematurely discontinuing the trial should perform the EoS/ED assessments.

EARLY DISCONTINUATION FROM RANDOMIZED TREATMENT

Patients who discontinue early from randomized treatment within a Treatment Cycle will have to complete the End of Treatment (EoT) assessments and complete the remaining visits in the current Treatment Cycle, according to the general schedule of assessments (SoA) (Table 1). These patients will not receive any further IMP administration during the trial and will continue to be followed for safety and disease severity (limited to MG-ADL and QMG) as per the SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

Patients who discontinue early from randomized treatment in the ITC period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per Table 2.

TEMPORARY INTERRUPTION FROM RANDOMIZED TREATMENT

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

A schematic of the trial design is presented in Figure 1.

4.2. Discussion of Trial Design

In the current trial, ARGX-113 will be administered in patients with gMG, with the aim to evaluate the efficacy, safety, tolerability and quality of life of ARGX-113.

This trial is designed as a randomized, double-blind, and placebo-controlled trial to distinguish the effect of ARGX-113 from other influences such as placebo effect or biased observation. The trial consists of a treatment part where all randomized patients will be treated with the IMP and a re-treatment part where patients may be re-treated with the IMP on an "as needed basis" in subsequent Treatment Cycles. The time between Treatment Cycles is based on the duration of the treatment effect and may vary from patient to patient and for each patient from cycle to cycle (patient-tailored approach).

Patients will continue to receive their SoC during the trial irrespective of the treatment they receive (ARGX-113 or placebo) which will be administered as an add-on therapy to the SoC. It 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 chosen primary endpoint in this trial is the percentage of patients who, after the first Treatment Cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to TC_1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in the active versus placebo group in AChR-Ab seropositive patients. The MG-ADL is a standardized 8-item patient-reported scale to assess MG symptoms and their effects on daily activities and is largely used by Investigators in several trials. MG-ADL is a widely used and validated tool to monitor the severity of MG and to assess the effect of treatment on the clinical manifestations of the disease. A reduction of at least 2 points of the MG-ADL is generally considered clinically meaningful (Wolfe, Herbelin et al. 1999; Muppidi, Wolfe et al. 2011).

All secondary endpoints are complementary to the primary endpoint. These endpoints provide more information related to specific aspects of the efficacy. The QMG test is a validated and widely used clinical tool to measure disease severity in MG patients. In contrast to MG-ADL, which is based on patient reporting, QMG provides quantitative assessments of symptoms / signs of the disease based on the Investigator's assessment (Barohn, McIntire et al. 1998; Katzberg, Barnett et al. 2014).

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 ARGX-113 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 ARGX-113.

The choice of the dose/regimen of ARGX-113 (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 ARGX-113-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

modelling, lower doses (e.g., 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 ARGX-113 administered weekly for 4 weeks seems to provide the best benefit/risk ratio and was selected for future trials.

All efficacy, quality of life and safety assessments used in this trial are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant.

4.3. Selection of Trial Population

4.3.1. Inclusion Criteria

Patients will be randomized 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 comply with the trial protocol procedures.
2. Male or female patients aged ≥ 18 years.
3. Diagnosis of MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the MGFA class II, III, IVa and IVb.

   The confirmation of the diagnosis should be documented and supported by at least 1 of the following 3 tests:

   - History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation, or
   - History of positive edrophonium chloride test, or
   - Patient has demonstrated improvement in MG signs on oral AChE inhibitors as assessed by the treating physician.
4. A total MG-ADL score of ≥ 5 points at Screening and Baseline (SEB) with more than 50% of the total score due to non-ocular symptoms.
5. Patients are required to be on a stable dose of their MG treatment (SoC) prior to Screening. The SoC is limited to AChE inhibitors, steroids and NSIDs. For patients receiving NSIDs, steroids, and/or AChE inhibitors as concomitant medications the following stability dose conditions will apply:

   - Non-steroidal immunosuppressive drugs (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months prior to Screening and no dose changes in the last 3 months before Screening.

- Steroids: treatment initiated at least 3 months prior to Screening and no dose changes in the last month before Screening.
- Acetylcholinesterase inhibitors: stable dose with no dose escalation in the past 2 weeks before Screening.

  Note: AChE inhibitors must be halted for at least 12 hours consistent with the revised manual for the QMG test as recommended by the MGFA, before the QMG assessment.

4.3.2. Exclusion Criteria

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

1. 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 (see DEFINITION OF TERMS) should have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (SEB) prior to administration of IMP.

   Note: Women of childbearing potential should use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month, of combined estrogen and progestogen hormonal contraception with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or agree upon continuous abstinence from heterosexual sexual contact.

2. 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.

   Note: Sterilized male patients who have had vasectomy with documented aspermia post-procedure, or male patients who have a partner of non-childbearing potential, can be included.

3. MGFA Class I and V patients.
4. Patients with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, fluoroquinolones, beta-blockers, etc.).
5. Patients with known seropositivity or who test positive for an active viral infection at Screening with:
   - Hepatitis B Virus (HBV) (except patients who are seropositive because of HBV vaccination)

- Hepatitis C Virus (HCV)
- Human Immunodeficiency Virus (HIV)

6. Patients with any known severe bacterial, viral or fungal infection or any major episode of infection that required hospitalization or injectable antimicrobial therapy in the last 8 weeks prior to Screening.
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 total IgG level < 6 g/L at Screening.
9. Patients with documentation of a lack of clinical response to PLEX.
10. Use of investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to Screening.
11. Immunoglobulins given by IV (IVIg), subcutaneous or intramuscular route, or PLEX, each within 1 month prior to Screening.
12. Patients who have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders, unless deemed cured by adequate treatment with no evidence of recurrence for ≥ 3 years before Screening. Patients with completely excised non-melanoma skin cancer (such as basal cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time.
13. Thymectomy when performed < 3 months prior to Screening or planned to be performed during the trial period.
14. Patients with clinical evidence of other significant serious 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.
15. Patients who previously participated in a clinical trial with ARGX-113.
16. Patients who received a vaccination (e.g., influenza vaccine) within the last 4 weeks prior to Screening.
17. Use of any monoclonal antibody, such as rituximab and eculizumab, within 6 months prior to first dosing.

4.4. Early Discontinuation

The criteria for screening and randomization are to be followed explicitly. If it is noted that a patient who does not meet one or more of the inclusion and/or meets one or more of the

exclusion criteria is inadvertently randomized and dosed, the Medical Monitor at Sponsor's Designated CRO and the Sponsor's Medical Director must be contacted immediately.

4.4.1. Early Discontinuation from Trial

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** and complete the EoS/ED visit if:

- they withdraw their consent
- the randomization code is broken prematurely by the Investigator or his/her staff
- 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 SoA (Table 1). Investigators will make and document all efforts made to 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.

4.4.2. Early Discontinuation from Randomized Treatment

Early discontinuation from randomized treatment means that the patient stops receiving the ongoing treatment and will never start a new Treatment Cycle for the entire duration of the trial; however informed consent is not withdrawn. These patients will continue to be followed up in the trial according to the SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

Patients **must** be discontinued early from randomized **treatment** if:

- Patient is pregnant
- Patients receives rescue therapy
- Patient develops an SAE that is likely to result in a life-threatening situation or pose a serious safety risk.
- Prohibited medication is taken (see Section 6.8.1)

Patients **might** discontinue early from randomized **treatment**:

- In case the 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 randomized treatment will depend on the evaluation on a case by case basis. Patients who, after evaluation of the above situations, are not discontinued from randomized treatment, may have a temporary interruption from randomized treatment (see Section 4.4.3).

Patients who discontinue early from randomized treatment within a Treatment Cycle will have to complete the EoT assessments and complete the remaining visits in the current Treatment Cycle, according to the general SoA (Table 1). These patients will not receive any further IMP administration during the trial and will continue to be followed for safety and disease severity (limited to MG-ADL and QMG) as per the SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

Patients who discontinue early from randomized treatment in the ITC period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per Table 2.

4.4.3. Temporary Interruption from Randomized Treatment

A patient that does not need to be discontinued early from randomized treatment might still have a temporary interruption from randomized treatment. A temporary interruption from randomized treatment is defined as a discontinuation of the current Treatment Cycle but the patient might still be eligible for further additional treatments with IMP within this trial.

Patients for whom treatment is interrupted will have to complete the current Treatment Cycle and will continue the trial as per general SoA (Table 1).

4.4.4. Missed Doses

Patients who miss one, two or three infusions per Treatment Cycle will stay in the trial and will follow the assessments as per general SoA (Table 1). These patients may be eligible for further Treatment Cycles during the trial.

4.5. Roll-Over to Follow-on Trial

At EoS, patients will be offered the option to roll over into a long-term, single-arm, open-label follow-on trial (ARGX-113-1705) where they will be treated with ARGX-113 (10 mg/kg of body weight) on an “as needed basis”.

Patients who need re-treatment but cannot complete a Treatment Cycle within the time frame of the ARGX-113-1704 trial (i.e., require re-treatment after Day 127), may roll over immediately to the follow-on trial to receive treatment with ARGX-113.

Patients who discontinue early from trial ARGX-113-1704, will not be offered the option to roll over in the follow-on trial.

Patients who discontinue 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 will also not be offered the option to roll over to the follow-on trial. Patients who discontinue early from randomized treatment for other reasons and patients who have a temporary interruption from randomized treatment may be offered the option to roll over to the follow-on trial.

4.6. 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 of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Regulatory Authority as per local regulation, except where necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (e.g., 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.

4.7. Screen Failures, Rescreening, and Retesting

Evaluations at Screening and confirmation at Visit 1 will be used to determine the eligibility of each patient for randomization at SEB (Visit 1). Patients who fail to meet the eligibility criteria will be considered screen failures.

Patients may be rescreened (i.e., redoing the full assessments as per general SoA, Table 1) or retested once (i.e., redoing 1 assessment) after Sponsor's written approval.

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

- Patients who required treatment for an acute illness (e.g., a urinary tract infection) or have a chronic medical problem (e.g., uncontrolled hypertension) may be rescreened once the illness resolved or the medical problem stabilized.

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

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

4.8. Early Termination of Trial or Site

The trial may be terminated at any time by the Sponsor for safety concerns due to serious adverse events (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.

4.9. End of Trial definition

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 Cycle visits (Visit 1 to Visit 9) and of ± 2 days for ITC visits. Every effort should be made to schedule every visit on the exact day (which is relative to the Baseline visit [SEB or TC_nB]) within the window as described in the general SoA (Table 1).

Each Treatment Cycle consists of 9 weekly visits over a period of 8 weeks, consisting of a Treatment period of 3 weeks (4 weekly infusions) and a FU period of 5 weeks.

The SEB and $TC_{[1]}B$ will both be set at randomization (Visit 1), whilst the Baseline of each subsequent Treatment Cycle (TC_nB) will be set at Visit 1 of each corresponding Treatment Cycle.

At all visits, the efficacy and quality of life assessments should be performed first, prior to any other trial-specific procedure with the only exception of obtaining informed consent at Screening and the weight assessment (if applicable). The MG-ADL scale needs to be performed prior to all other efficacy or quality of life assessments (QMG, MGC, EuroQoL 5 Dimensions 5 Levels [EQ-5D-5L] and MG-QoL15r). 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 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).

Patients who discontinue early from randomized treatment, after they have completed the EoT assessments and, if applicable, the remaining visits of the current Treatment Cycle, will return every month (30 ± 3 days) for Follow-up visits until Day 182 as per SoA for Patients who Discontinued Early from Randomized Treatment (Table 2). These patients will then continue in the trial to be followed for safety and disease severity (limited to MG-ADL and QMG).

5.1. Informed Consent

The patient must sign the informed consent form (ICF) prior to any trial-related assessment.

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.

Any patient who provides informed consent is being assigned a patient identification number.

5.2. Screening

After informed consent has been obtained, patients will be screened at the site for eligibility 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, the following assessments will be performed at Screening:

- Assign patient identification number.
- Eligibility evaluation (review of in- and exclusion criteria).
- Clinically relevant medical and surgical history, clinically relevant prior treatment and all concomitant medications (see Sections 7.2.5 and 6.8).
- Demographic characteristics (date of birth, sex, race, and ethnicity, per national regulations).
- The efficacy assessment MG-ADL should be done prior to any other trial-specific assessment at Screening, except for obtaining informed consent and the weight assessment. A total MG-ADL score ≥ 5 with more than 50% of this total score attributed to non-ocular symptoms should be met at Screening.
- Suicidal ideation and behavior will be assessed via a targeted question based on the Patient Health Questionnaire item 9 (PHQ-9) (Simon, Rutter et al. 2013).

- Complete physical examination, including at a minimum: general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological systems.
- Height and weight.
- Vital signs (supine blood pressure, heart rate, body temperature). It is recommended that the method used to measure body temperature at Screening is maintained throughout the trial for each patient.
- Electrocardiogram (ECG) (heart rate, PR, QT and QRS interval).
- Clinical laboratory tests (see Appendix 6 for an overview of the clinical laboratory tests that will be assessed). In addition, total IgG will be assessed at central lab for defining eligibility. Patients need to be fasted at least 8 hours prior to sampling.
- Sampling to determine the AChR/MuSK-Ab serotype (seronegative or seropositive) of the patient. In case the AChR-Ab result is not available in time (i.e. within the 2 weeks screening window), the screening window can be enlarged on an ad-hoc base with maximum 5 calendar days.
- Urinalysis.
- Serum pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS).
- Viral tests (see Appendix 6 for more details).
- Assess AEs if any.

5.3. Randomization

The results of all Screening procedures required to determine eligibility must be available prior to randomization at Visit 1 of the first Treatment Cycle (TC_1B).

The following assessments should be performed at Visit 1 of the first Treatment Cycle (randomization visit):

- Eligibility evaluation (review of specified in- and exclusion criteria).(*)
- Efficacy and quality of life assessments should be performed prior to any other trial-specific assessment, except for the weight assessment (if applicable), with the MG-ADL scale to be performed prior to all other efficacy or quality of life assessments (QMG, MGC, EQ-5D-5L and MG-QoL15r). A total MG-ADL score ≥ 5 with more than 50% of this total score attributed to non-ocular symptoms should be met at Visit 1 (SEB). If the total MG-ADL score differs from the one at Screening, the total score at SEB will be taken into account for the analyses.(*)

- 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.(*)
- Electrocardiogram.(*)
- 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).(*)
- Anti-drug antibodies (ADA).(*)
- Pharmacokinetic sampling within 1 hour prior to start of infusion(*) and within 1 hour after the end of infusion.
- Administration of the IMP (ARGX-113 or placebo) 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 the IMP (pre-dose).

Randomization should be performed as soon as possible after Screening in approximately 2 weeks with a possible ad-hoc extension of maximum 5 calendar days in case of non-availability of AchR AB status, however only after confirmation of eligibility of the patient. If a patient meets all the trial eligibility criteria and after approval from the Sponsor, he/she will be stratified via Interactive Response Technology (IRT) according to 3 stratification factors: Japanese vs. non-Japanese patients, AChR-Ab status (seropositive vs. seronegative) and SoC (patients on NSIDs vs. patients not on NSIDs). Within each stratum, the patient will be randomized (1:1) via IRT to be treated with either placebo or ARGX-113, on top of their current SoC. A maximum of 20% AChR-Ab seronegative patients will be allowed in the trial. If the patient is not eligible, then he/she should be recorded as a screen failure in the EDC system.

5.4. Treatment Cycle

5.4.1. Treatment Period

After randomization (including Visit 1 of the first Treatment Cycle; see Section 5.3), the following assessments will be performed at Visit 2 to Visit 4 of the first Treatment Cycle and at Visit 1 to Visit 4 of the subsequent Treatment Cycles.

- Efficacy and quality of life assessments should be performed prior to any other trial-specific assessment, except for the weight assessment (if applicable), with the MG-ADL scale to be performed prior to all other efficacy or quality of life assessments (QMG, MGC, EQ-5D-5L and MG-QoL15r).(*)
- 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.(*)
- Electrocardiogram.(*)
- 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).(*)
- Anti-drug antibodies at Visit 4 of the first Treatment Cycle. As from the second Treatment Cycle onwards, samples for ADA will only be taken at Visit 1 of the corresponding Treatment Period.(*)
- Pharmacokinetic sampling within 1 hour prior to start of infusion(*) and within 1 hour after the end of infusion.
- Administration of the IMP (ARGX-113 or placebo) 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 the IMP (pre-dose).

At Visit 1 of each subsequent Treatment Cycle, the conditions for re-treatment will be checked before administration of the IMP (see Section 4.1).

Patients may not receive re-treatment with ARGX-113 or placebo if, at the time of re-treatment, patients 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 and will be discontinued early from randomized treatment to receive appropriate alternative MG treatment.

For the entire duration of the trial, a change in the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency) is not allowed.

5.4.2. Follow-up Period

The FU period within a Treatment Cycle will include weekly assessments starting at Visit 5 up to Visit 9 of the corresponding Treatment Cycle.

The following assessments will be performed:

- Efficacy and quality of life assessments should be performed prior to any other trial-specific assessment, except for the weight assessment (if applicable), with the MG-ADL scale to be performed prior to all other efficacy or quality of life assessments (QMG, MGC, EQ-5D-5L and MG-QoL15r).
- 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.
- Electrocardiogram.
- 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).

- Anti-drug antibodies at Visits 6 and 9 from the first Treatment Cycle. As from the second Treatment Cycle onwards, samples for ADA will only be taken at Visit 9 of the corresponding FU period.
- Pharmacokinetic sampling (only at Visits 5 and 6).
- Review of concomitant medication and rescue therapy.
- Assess AEs if any.

5.5. Inter Treatment Cycle Period

The ITC period will consist of visits every 2 weeks, starting 14 days (± 2 days) from the last visit of the previous Treatment Cycle.

At each ITC_nV, an evaluation of the need for re-treatment should be done. In case the patient is not in need of re-treatment, assessments for ITC_nV should be performed as listed below and per general SoA (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 TC_nV1 are to be performed instead.

The following assessments will be performed:

- Efficacy and quality of life assessments should be performed prior to any other trial-specific assessment, except for the weight assessment (if applicable), with the MG-ADL scale to be performed prior to all other efficacy or quality of life assessments (QMG, MGC, EQ-5D-5L and MG-QoL15r).
- 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.
- Electrocardiogram.
- 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.

5.6. End of Treatment

Patients who do **not discontinue early from randomized treatment** will perform the assessments on Visit 4 of the last Treatment Cycle as indicated in the general SoA (Table 1) (see Section 5.4.1).

For patients who **discontinue early from randomized treatment**, the assessments will depend on the visit at which it was decided that the patient had to discontinue early from randomized treatment.

Patients who discontinue early from randomized treatment **within a Treatment Cycle** will perform the planned assessments of that corresponding visit (see Section 5.4), and complete the remaining visits in the current Treatment Cycle according to the general SoA (Table 1). These patients will not receive any further IMP administration during the trial and will continue to be followed for safety and disease severity (limited to MG-ADL and QMG) as per the SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

Patients who discontinue early from randomized treatment **in the ITC period** will perform the planned assessments of the current ITC visit as per Table 1 (see Section 5.5), prior to entering the Safety and Disease Severity Follow-up period as per SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

5.7. Safety and Disease Severity Follow-up Period for Patients who Discontinued Early from Randomized Treatment

After the decision of early discontinuation from randomized treatment, and after the patient completed either the current Treatment Cycle, or the EoT assessments of the current ITC visit if the decision was made in the ITC period, the patient should return every month for FU visits until Day 182 as per SoA for Patients who Discontinued Early from Randomized Treatment (Table 2).

The following assessments will be performed:

- Assessments of disease severity. MG-ADL scale needs to be performed prior to the QMG scale and prior to any other assessments.
- Urine pregnancy test (only for women of childbearing potential, see DEFINITION OF TERMS).
- Review of concomitant medication and rescue therapy.
- Assess AEs if any.

5.8. 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 182) must be performed as follows:

- Efficacy and quality of life assessments should be performed prior to any other trial-specific assessment, except for the weight assessment (if applicable), with the MG-ADL scale to be performed prior to all other efficacy or quality of life assessments (QMG, MGC(*), EQ-5D-5L(*) and MG-QoL15r(*)).
- Suicidality assessment.(*)
- Physical examination.(*)
- Weight.(*)
- Vital signs.(*)
- Electrocardiogram.(*)
- 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).(*)
- Anti-drug antibodies.(*)
- Pharmacokinetic sampling.(*)
- Review of concomitant medication and rescue therapy.
- Assess AEs if any.

(*) Only applicable for patients following Table 1.

5.9. Unscheduled Visit

It is at the Investigator's discretion, or on request of the patient, 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 TREATMENTS

6.1. Treatments Administered

ARGX-113 or matching placebo 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 Cycle. A variation of ± 10% of the amount, as planned per protocol, of ARGX-113 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 ARGX-113 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, ARGX-113 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 Products

The IMP (ARGX-113 or placebo) 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.

CCI

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

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

6.3. Packaging and Labeling

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

6.4. Storage of Investigational Medicinal Products

The Investigator (or his/her designee) is responsible for the correct and safe storage of the IMP assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the IMP, and maintained within the appropriate temperature ranges. The IMP must be stored as specified at delivery and in the original packaging. The placebo and ARGX-113 labeling and packaging will be identical.

The IMP 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

Once the patient has provided informed consent and eligibility has been confirmed by the Sponsor, patients will be stratified according to 3 stratification factors: Japanese vs. non-Japanese patient, AChR-Ab status (seropositive vs. seronegative) and SoC (patients on NSIDs vs. patients not on NSIDs) and randomized at Visit 1 of the first Treatment Cycle via IRT within each stratum to be treated with either ARGX-113 or placebo, on top of their current SoC. A maximum of 20% AChR-Ab seronegative patients will be allowed in the trial. A patient identification number will be allocated, and upon confirmation of eligibility at Visit 1 of the first Treatment Cycle, the site, after confirmation by the Sponsor, will randomize the patient via IRT, which will assign a patient randomization number.

Definition: A Japanese patient is defined as a patient whose parents and four grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of > 10 years and currently lives in Japan.

The randomization code will be held by the IRT vendor. Patients will be randomized in a 1:1 ratio to ARGX-113 or placebo. No blinded trial team members from the Sponsor or the Sponsor's designated blinded CRO team will have access to this randomization code until after final database lock.

6.6. Timing of Dose for Each Patient

ARGX-113 or placebo will be administered IV over a period of 1 hour as 4 weekly infusions at Visits 1, 2, 3, and 4 of each Treatment Cycle. 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 Cycle.

6.7. Blinding

This is a randomized, double-blind, placebo-controlled trial with limited access to the randomization code. ARGX-113 and placebo will be identical in physical appearance. The treatment that each patient receives will not be disclosed to the Investigator, investigational site staff, patient, Sponsor, and the Sponsor's designated CRO. The trial will only be unblinded following the database lock, except in the situation of unblinding for safety reasons.

Emergency Unblinding Procedure

Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via IRT, which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of an AE for which it is necessary to know the randomized treatment to determine an appropriate course of therapy for the patient. The Investigator should first discuss options immediately with the Medical Monitor and Sponsor if possible with due consideration of the safety of the patient. If the Investigator must identify the treatment assignment of an individual patient, the Principal Investigator/Sub-Investigator is to contact the IRT.

Patients for whom the code has been broken by the Investigator will have to be discontinued from the trial and all efforts must be made to conduct the ED visit.

Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and eCRFs.

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 must be recorded in the eCRFs. 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.

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

6.8.1. Prohibited Medications during the Trial

The following medications or treatments will lead to discontinuation from randomized treatment:

- Any IgG therapy
- A change in the type or dose/regimen of SoC (replacing, adding or removing SoC, or adjustment of the SoC dose and/or frequency), 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

6.8.2. Rescue Therapy

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 one 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 randomized treatment.

6.9. Medical Care of Patients after End of Study

After a patient has completed the trial and will not roll over into the follow-on trial ARGX-113-1705, 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 neither will the IMP be provided on a compassionate use program.

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 IMP administration and any deviations from the intended regimen must be recorded.

6.11. Handling Missed Doses of the Investigational Medicinal Product

Patients will receive 4 weekly IV infusions of IMP at a dose of 10 mg/kg over a period of 1 hour during each Treatment Cycle.

All efforts will be done to ensure that the patient receives the 4 administrations of IMP within the allowed time windows. However, if a patient misses 1 or more doses in any Treatment Cycle, the patient will not be discontinued early from the trial or from further randomized treatment and will complete all further visits and assessments according to the general SoA (Table 1). This patient may be eligible for further Treatment Cycles during the trial.

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

6.12. Accountability of Investigational Medicinal Product

Detailed instructions on accountability of the IMP 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 ARGX-113 or MG, unless this would not be allowed according to local regulations or the patient would not agree.

7. TRIAL ASSESSMENTS

7.1. Efficacy and Quality of Life

Efficacy assessments will be assessed using MG-ADL, QMG, and MGC, and quality of life will be measured using MG-QoL15r and EQ-5D-5L. All these assessments have to be performed pre-dose on all IMP infusion days and following the order specified in the general SoA (Table 1), and prior to any other assessment at each visit except for the assessment of weight (if applicable) and signing of the ICF at the Screening visit.

The MG-ADL, QMG, and MGC assessments for a given patient are preferentially assessed by one and the same trained evaluator throughout the course of the trial whenever possible.

For patients who are unable to read and write, the patient questionnaires MG-QoL15r and EQ-5D-5L can be completed by a caregiver. In that case, the caregiver should read out loud the questions (without given any personal interpretation or explanation to the patient) and complete the exact answer as given by the patient.

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 arising from the 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 (WHO 2001).

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.

7.1.3. Myasthenia Gravis Composite

The MGC has 10 items (Appendix 3) combining a trained rater's examination and patient reported outcomes. The 2 ocular items are derived from QMG. It has 3 items on muscle strength (deltoids, hip flexors, and neck flexors or extensors) and 4 items on bulbar function (swallowing, chewing, breathing, and speech functions), based on the clinical history. Each item is scored on an ordinal scale with 4 possible categories, but the items are weighted, whereby bulbar impairments weigh more than ocular ones. The impairments that need to be examined by the Investigator include ptosis or upward gaze, double vision, eye closure, neck flexion, shoulder abduction, and hip flexion. The patient reported outcomes under MGC are talking, chewing, swallowing, and breathing. The maximum total possible score is 50, with

higher total scores reflecting more severe impairments. The scoring of MGC should be performed by a trained evaluator.

7.1.4. 15-Item Quality of Life Scale for Myasthenia Gravis

The MG-QoL15r (Appendix 4) is a quality of life scale or survey of patient's responses and addresses MG-specific psychological well-being and social functioning. It is a brief questionnaire that is to be completed by the patient that uses 3 response options. The MG-QoL15r is helpful in informing the clinician about the patient's perception of the extent of and dissatisfaction with MG-related dysfunction. Each item is scored from 0 to 2 according to its frequency, with a maximum total score of 30.

7.1.5. EQ-5D-5L

EQ-5D (5 level version) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Appendix 5). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. A unique health state is defined by combining 1 level from each of the 5 dimensions. A total of 3125 possible health states is defined in this way. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

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; and other tests that are deemed critical to the safety evaluation of the trial in all patients who receive at least 1 dose of the IMP. 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 IMP, whether or not considered related to the medicinal product or IMP.

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 (i.e., ECG) should not be reported as AEs unless they are considered clinically significant, e.g., require therapy (e.g., 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 an IMP, 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 IMP 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 IMP, 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 one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., 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 the IMP 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 IMP, whether considered related to the IMP or not. TEAEs are recorded from the start of IMP administration, until completion of the patient's last visit.

Overdose

For the purposes of this trial, exceeding the dosage requirements specified in this protocol represents an overdose (see Section 6.1). 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 noninvasive 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 the IMP/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 the IMP caused the AE.
- An "unlikely" relationship suggests that only a remote connection exists between the IMP 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 IMP, it follows a known or expected response pattern to the IMP, 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 the IMP 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 of 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.

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.

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. 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 IMP, 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 the IMP, 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 is 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 IMP 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.

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 IRB/IEC 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 EoS 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 IMP 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 EoS visit are to be collected and reported as previously described (as per Section 7.2.1.1) 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 (e.g., 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

Serum pregnancy tests will be performed centrally at Screening. Urine pregnancy tests will be conducted and analyzed locally before randomization and thereafter at visits as detailed in the general SoA (Table 1).

If a patient becomes pregnant after the administration of IMP and up to 90 days after the patient received the last infusion, the Sponsor and/or Sponsor's designee should be informed immediately (i.e., 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 randomized treatment.
- The patient should have EoT assessments.
- All assessments for EoT (see Sections 4.4.2 and 5.6) 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 IMP. 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 the IMP.

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

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, PK, PD, viral testing, and ADA will be analyzed at a central lab as indicated in the general SoA (Table 1) and Appendix 6. Patients need to be fasting for at least 8 hours prior to the sampling for clinical laboratory tests as from Screening up to EoS. Retesting is allowed once after Sponsor's written approval (see Section 4.7).

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

For all patients of childbearing potential, a serum pregnancy test will be performed centrally at Screening (on the samples taken for clinical laboratory tests), and a urine pregnancy test will be conducted and analyzed locally at the site (on the urine samples taken for urinalysis) at all visits, except at Screening.

The estimated total maximum blood volume needed for a patient during the trial (when completing the trial up until the last visit) is between 225 mL for a patient who receives 1 Treatment Cycle only and 385 mL for a patient who receives the maximum of 3 treatment cycles.

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.

Besides the urine pregnancy test which will be conducted and analyzed locally, all samples will be analyzed centrally.

CCI

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 SoA (Table 1) (pre-dose 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 Screening 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.

Height will be measured at Screening only and weight will be measured at Screening and at the EoS/ED visit. Weight measurement can be repeated at any visit when there is an obvious weight change compared to the last weight assessment. For the assessment of height and weight, patients will be required to remove their shoes and wear light indoor clothing for these measurements.

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.

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 (Simon, Rutter et al. 2013).

7.2.5. Medical and Surgical History

Clinically significant findings and pre-existing conditions present in a patient prior to Screening 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 Screening.

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 unblinded safety data (including the overall number of patients treated up to that point, rates, and patient-level details) and determine if there is an imbalance in the treatment arms with respect to these events, based on clinical judgment of the DSMB. 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 DSMB. 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. Pharmacokinetics (PK)

Blood samples for PK will be collected from each patient as presented in Table 1. Concentrations of ARGX-113 will be determined using a validated assay. The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF.

7.4. Pharmacodynamics (PD)

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.

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.

7.5. Anti-Drug Antibodies (ADA)

Blood samples to assess ADA will be collected pre-dose at the time points as indicated in Table 1. At Baseline (SEB and TC_nB), Screening, 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.

8.1. Determinations of Sample Size

The null hypothesis H0 states that there is no difference in proportion of MG-ADL responders between patients treated with placebo and ARGX-113. The trial is powered at 90% using significance level of 5% 2-sided to test the alternative hypothesis of that the difference in the proportion of responders is 29% in favor of patients treated with ARGX-113. The 29% is a weighted average of 80% AChR-Ab seropositive patients with treatment difference of 35% and 20% AChR-Ab seronegative patients with treatment difference of 5%. The proportion MG-ADL responders amongst patients treated with placebo is hypothesized to be 30%. In order to test this alternative hypothesis, a sample size of 150 patients is needed, with this allowing for 10% attrition rate.

8.2. Analysis Populations

The efficacy analyses will be done in the modified Intention-To-Treat (mITT: all randomized patients who have a Baseline efficacy total score for MG-ADL and at least one post-Baseline total MG-ADL score) and in the Per Protocol (PP) populations for sensitivity analyses of primary and secondary endpoints. PP is defined as subset of mITT, i.e., all randomized patients who have a Baseline efficacy total score for MG-ADL and at least one post-Baseline total MG-ADL score and that received at least 3 out of 4 infusions (in any order), and without a major protocol deviation. Safety analysis will be performed on safety set comprising all patients in the randomized population who received at least one dose or part of a dose. The safety analysis will be based on the actual treatment received.

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 screened, randomized, completed, as well as the number of early discontinuations from randomized treatment (including rescued patients) and trial, with reasons for discontinuation from treatment or trial, and major protocol deviations.

A listing will be presented to describe dates of Screening, randomization or assigned treatment, screen failure with reason, completion or early discontinuation and the reason for discontinuation, if applicable, for each patient.

Patient characteristics will be recorded prior to randomization and will be listed and summarized by treatment. Overall summaries will include descriptive statistics for continuous measures (number of observations, mean, standard deviation, median, minimum and maximum) and for categorical measures (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 by treatment with frequency and percentage. All concomitant medications used will be listed.

8.4. Statistical Methods

8.4.1. Primary Endpoint Analyses

The primary endpoint is tested by means of a 2-sided exact test (using logistic regression) stratified for the stratification factors Japanese vs non-Japanese patients, AChR-Ab serotype and SoC at the 2-sided 5% significance level, in the AChR-Ab seropositive patients. Percentage MG-ADL responders will be compared between ARGX-113 and placebo using logistic regression model with Baseline total score as covariate and Japanese/non-Japanese patient, AChR-Ab serotype and SoC as stratification variables.

The treatment effect will be presented as the odds ratio together with its 95% confidence interval (CI) and 2-sided p-value.

8.4.2. Secondary Endpoint Analyses

The primary efficacy endpoint will be tested at the 5% 2-sided alpha level and will act as gatekeeper for the testing of secondary endpoints. Subject to meeting significance for the primary endpoint, secondary endpoints will be tested at the 5% 2-sided significance level in a strict **hierarchical order** as follows:

Secondary endpoints:

1. Comparison of proportion responders based on QMG between active and placebo group after the first Treatment Cycle, in AChR-Ab seropositive patients.
2. Comparison of proportion responders based on MG-ADL between active and placebo group after the first Treatment Cycle, in overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).
3. Comparison of proportion of time that patients have a "clinically meaningful improvement" in total MG-ADL score between active and placebo group in AChR-Ab seropositive patients.
4. Time from start of TC_1V5 to qualification for re-treatment monitored by total MG-ADL score between active and placebo group in AChR-Ab seropositive patients if:
   - the patient has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms, and
   - no clinically meaningful improvement (decrease in total MG-ADL score from $TC_1B < 2$).
5. Comparison of percentage early MG-ADL responders based on the total MG-ADL score between active and placebo group after the first Treatment Cycle, in AChR-Ab seropositive patients.

Secondary endpoints n°1, n°2 and n°5 will be analyzed using the same statistical approach as described for the analysis of the primary endpoint. Secondary endpoint n°3 will be analyzed using an analysis of covariance (ANCOVA) model with terms for randomized treatment and Baseline total MG-ADL score as a covariate; the model will be stratified for the stratification variables. Secondary endpoint n°4 will be analyzed using Kaplan-Meier time to event analysis (stratified log-rank test), stratified for the stratification variables.

8.4.3. Tertiary Endpoint Analyses

The **tertiary** endpoints will be analyzed in a descriptive manner.

Summary statistics will be provided for the continuous endpoints in terms of absolute values and changes from Baseline (SEB and TC_nB).

In addition, difference in total score change from Baseline between treatment groups at the different post-Baseline (SEB and TC_nB) time points will be analyzed by means of Mixed Models for Repeated Measurements (MMRM) (using all available data at all time points). The model will include treatment, visit and treatment by visit interaction terms as fixed effects, with Baseline value as a covariate; the analysis will be stratified for randomization strata. An unstructured (UN) covariance matrix for the repeated measures within patient will be specified for the analysis and the following statistics will be presented for each visit:

- Least Square (LS) Means per treatment group
- Standard error of LS Means
- 95% CI
- LS Mean Difference (ARGX-113 – placebo)
- Standard error of LS Mean Difference
- 95% CI for LS Mean Difference
- 2-sided p-value for testing differences between treatment groups

If the model does not converge upon using UN, the following covariance structures will be tested for convergence: heterogeneous Toeplitz (TOEPH), heterogeneous autoregressive 1 (ARH[1]), heterogeneous compound symmetry (CSH), TOEP, AR(1) and CS covariance structures.

Percentage of time that patients have a clinically meaningful improvement during the trial, will be analyzed using an ANCOVA model similar to that described for the percentage of time showing a clinically meaningful improvement.

The tertiary endpoints “MG-ADL responders from the second Treatment Cycle on (compared to each corresponding TCB) in AChR-Ab seropositive patients and in overall population”, and “QMG responders from the second Treatment Cycle on (compared to each corresponding TCB) in AChR-Ab seropositive patients”, will be analyzed using the same methodology as for the primary endpoint.

Frequency tables will also be presented for all binary variables, including AEs.

In addition, descriptive statistics will be provided for PD (IgG and subtypes, and also anti-AChR and anti-MuSK antibodies), PK and ADA.

ARGX-113 serum concentration data will be summarized and PK calculations will be performed with standard non-compartmental methods. The following PK parameters will be calculated after single and multiple administrations of ARGX-113 using individual concentration data in serum and actual sampling times:

C_{max}: maximum observed serum concentration

C_{trough}: serum concentration observed pre-dose at Visits 2, 3 and 4

R_{ac}: accumulation ratio, calculated as Visit 4 C_{max} /Visit 1 C_{max}

8.5. Interim Analyses

Not applicable

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 efficacy and safety 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, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects 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.

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 captured, 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, IRT provider, or centralized ECG reading. This 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 (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.

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 is screened. 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 Screening 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 IMP. 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 (records and documents pertaining to the conduct of this trial and the distribution of IMP, including 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 the IMP. The Sponsor will notify the Principal Investigator of these events.

These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the 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 IMP, 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 ARGX-113 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

1. Barohn, R. J., Herbelin, L. (2000). "The Quantitative Myasthenia Gravis Test Manual, Myasthenia Gravis Foundation of America, Inc. Revised March 25, 2000. University of Texas, Southwestern Medical Center, Dallas, Texas.", from http://myasthenia.org/LinkClick.aspx?fileticket=9U5kP6SfCJs%3D&tabid=125.
2. Barohn, R. J., D. McIntire, L. Herbelin, et al. (1998). "Reliability testing of the quantitative myasthenia gravis score." Ann N Y Acad Sci 841: 769-772.
3. Benatar, M., D. B. Sanders, T. M. Burns, et al. (2012). "Recommendations for myasthenia gravis clinical trials." Muscle Nerve 45(6): 909-917.
4. Burns, T. M., C. K. Grouse, M. R. Conaway, et al. (2010). "Construct and concurrent validation of the MG-QOL15 in the practice setting." Muscle Nerve 41(2): 219-226.
5. Burns, T. M., C. K. Grouse, G. I. Wolfe, et al. (2011). "The MG-QOL15 for following the health-related quality of life of patients with myasthenia gravis." Muscle Nerve 43(1): 14-18.
6. Challa, D. K., U. Bussmeyer, T. Khan, et al. (2013). "Autoantibody depletion ameliorates disease in murine experimental autoimmune encephalomyelitis." MAbs 5(5): 655-659.
7. Challa, D. K., R. Velmurugan, R. J. Ober, et al. (2014). "FcRn: from molecular interactions to regulation of IgG pharmacokinetics and functions." Curr Top Microbiol Immunol 382: 249-272.
8. Drachman, D. B. (1994). "Myasthenia gravis." N Engl J Med 330(25): 1797-1810.
9. EuroQoL. (2009). "EQ-5D-5L. Health Questionnaire. UK." from https://euroqol.org/wp-content/uploads/2016/10/Sample_UK__English__EQ-5D-5L_Paper_Self_complete_v1.0__ID_24700.pdf.
10. Gilhus, N. E. (2016). "Myasthenia Gravis." N Engl J Med 375(26): 2570-2581.
11. Gilhus, N. E. and J. J. Verschuuren (2015). "Myasthenia gravis: subgroup classification and therapeutic strategies." Lancet Neurol 14(10): 1023-1036.
12. Howard, J. F., Jr., R. J. Barohn, G. R. Cutter, et al. (2013). "A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis." Muscle Nerve 48(1): 76-84.
13. Howard, J. F., Jr., K. Utsugisawa, M. Benatar, et al. (2017). "Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study." Lancet Neurol 16(12): 976-986.
14. Kaminski, H. J. (2016). "Seronegative Myasthenia Gravis-A Vanishing Disorder?" JAMA Neurol 73(9): 1055-1056.
15. Katzberg, H. D., C. Barnett, I. S. Merkies, et al. (2014). "Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial." Muscle Nerve 49(5): 661-665.
16. Liu, J. F., W. X. Wang, J. Xue, et al. (2010). "Comparing the autoantibody levels and clinical efficacy of double filtration plasmapheresis, immunoadsorption, and intravenous immunoglobulin for the treatment of late-onset myasthenia gravis." Ther Apher Dial 14(2): 153-160.
17. Meriggioli, M. N. and D. B. Sanders (2009). "Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity." Lancet Neurol 8(5): 475-490.

18. Muppidi, S., G. I. Wolfe, M. Conaway, et al. (2011). "MG-ADL: still a relevant outcome measure." Muscle Nerve 44(5): 727-731.
19. Nowak, R. J., D. B. Dicapua, N. Zebardast, et al. (2011). "Response of patients with refractory myasthenia gravis to rituximab: a retrospective study." Ther Adv Neurol Disord 4(5): 259-266.
20. Patel, D. A., A. Puig-Canto, D. K. Challa, et al. (2011). "Neonatal Fc receptor blockade by Fc engineering ameliorates arthritis in a murine model." J Immunol 187(2): 1015-1022.
21. Roopenian, D. C. and S. Akilesh (2007). "FcRn: the neonatal Fc receptor comes of age." Nat Rev Immunol 7(9): 715-725.
22. Sadjadi, R., M. Conaway, G. Cutter, et al. (2012). "Psychometric evaluation of the myasthenia gravis composite using Rasch analysis." Muscle Nerve 45(6): 820-825.
23. Simon, G. E., C. M. Rutter, D. Peterson, et al. (2013). "Does response on the PHQ-9 Depression Questionnaire predict subsequent suicide attempt or suicide death?" Psychiatr Serv 64(12): 1195-1202.
24. Vaccaro, C., J. Zhou, R. J. Ober, et al. (2005). "Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels." Nat Biotech 23(10): 1283-1288.
25. Vincent, A., B. Lang and K. A. Kleopa (2006). "Autoimmune channelopathies and related neurological disorders." Neuron 52(1): 123-138.
26. WHO. (2001). "World Health Organization. International Classification of Functioning, Disability, and Health (ICF). 1st edition. World Health Organization 2001.", from http://www.who.int/classifications/icf/en/. .
27. Wolfe, G. I., L. Herbelin, S. P. Nations, et al. (1999). "Myasthenia gravis activities of daily living profile." Neurology 52(7): 1487-1489.
28. Wolfe, G. I., H. J. Kaminski and I. B. Aban, et al (2016). "Randomized Trial of Thymectomy in Myasthenia Gravis." N Engl J Med 375(6): 511-522.

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 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, 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 (Wolfe, Herbelin et al. 1999; Muppidi, Wolfe et al. 2011)

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	Spontaneo	____
Ptosis (upward gaze), seconds	61	11–60	1–10	Sp neous	____
Facial muscles	Normal lid closure	Complete, weak, some resistance	Compl without resi e	Inco ete	____
Swallowing 4 oz. water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe co ing g or reg itation	Cannot swallow (not mpted)	____
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarth at 30–49	D rthria 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	≥8	65–	50–64	<50	____
Right-hand grip, kgW					
Men	≥45		5–14	0–4	____
Women	≥30	10–	5–9	0–4	____
Left-hand grip, kgW					
Men	≥	5–34	5–14	0–4	____
Women	≥	10–24	5–9	0–4	____
Head lifted (45 degr pine), seconds	20	30–119	1–29	0	____
Right l utstretched (45 deg supine)	100	31–99	1–30	0	____
Left leg d (45 degree supine), seconds	100	31–99	1–30	0	____
			Total QMG score (range, 0–39)		

Source: website MGFA, Quantitative MG score (Barohn, McIntire et al. 1998; Katzberg, Barnett et al. 2014)

Appendix 3 Myasthenia Gravis Composite Scale

MG composite scale

Ptosis, upward ease (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 2	Immediate = 3
Double vision on lateral Gaze, left or right (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moder[illegible] weakness (can be f[illegible] easily) = 1	Severe weakness (unable to keep [illegible] closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = [illegible]	Constant slurring [illegible]asal but can be [illegible]derstood = [illegible]	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigu[illegible]th solid fo[illegible]d = 2	Fatig[illegible]th soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	R[illegible]isode [illegible] ch[illegible]ing[illegible] troub. swa[illegible]wi[illegible] 2	Frequent trouble swallowing, for example necessitating change in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Sho[illegible] of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension ([illegible]t) (physic[illegible] examination)	Norm[illegible]	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3	Severe weakness = 4
Shoul[illegible]abd[illegible]al (physician examination)	N[illegible]al = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
TOTAL				_____

Note: Please note that "moderate weakness" for neck and limb items should be construed as weakness that equals roughly 50% ± 15% of expected normal strength. Any weakness milder than that would be "mild," and any weakness more severe than that would be classified as "severe."

Source: website MGFA, MG composite scale (Benatar, Sanders et al. 2012; Sadjadi, Conaway et al. 2012)

Appendix 4 Revised Version of 15-Item Quality of Life Scale for Myasthenia Gravis (MG-QoL15r)

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limi ions … performing my work (inc le w… … home) bec… … my MG.			
9. I ha difficult… king e to MG			
10. I have lost some per nal independence becaus… my MG (e.g. driving, shop… …ning errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

Total MGQOL-R score

Source: website MGFA, MG-QoL15r (Burns, Grouse et al. 2010; Burns, Grouse et al. 2011)

Appendix 5 EQ-5D-5L (UK English Sample Version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

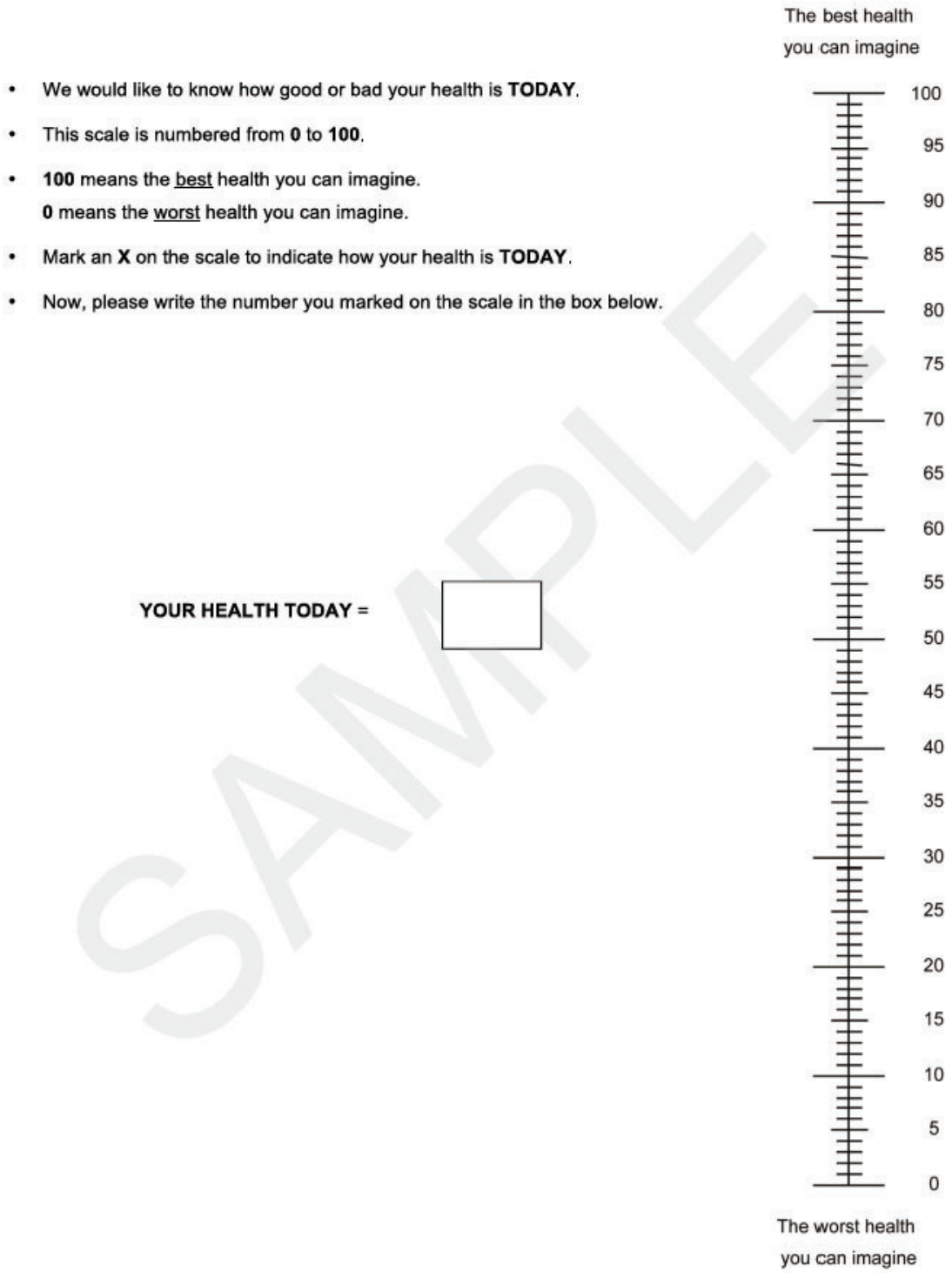
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

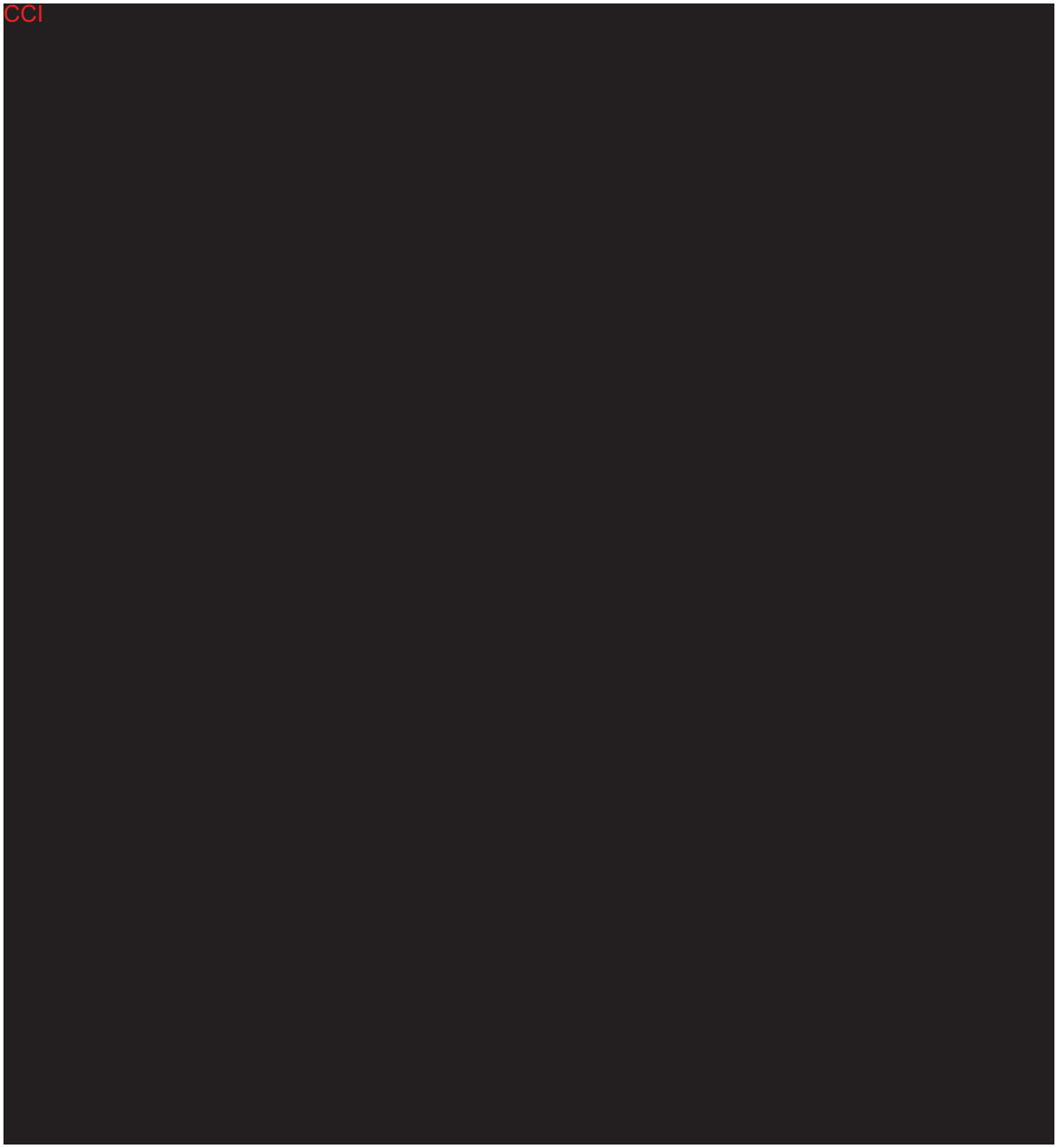


Source: website EuroQoL, EQ-5D-5L(EuroQoL 2009)

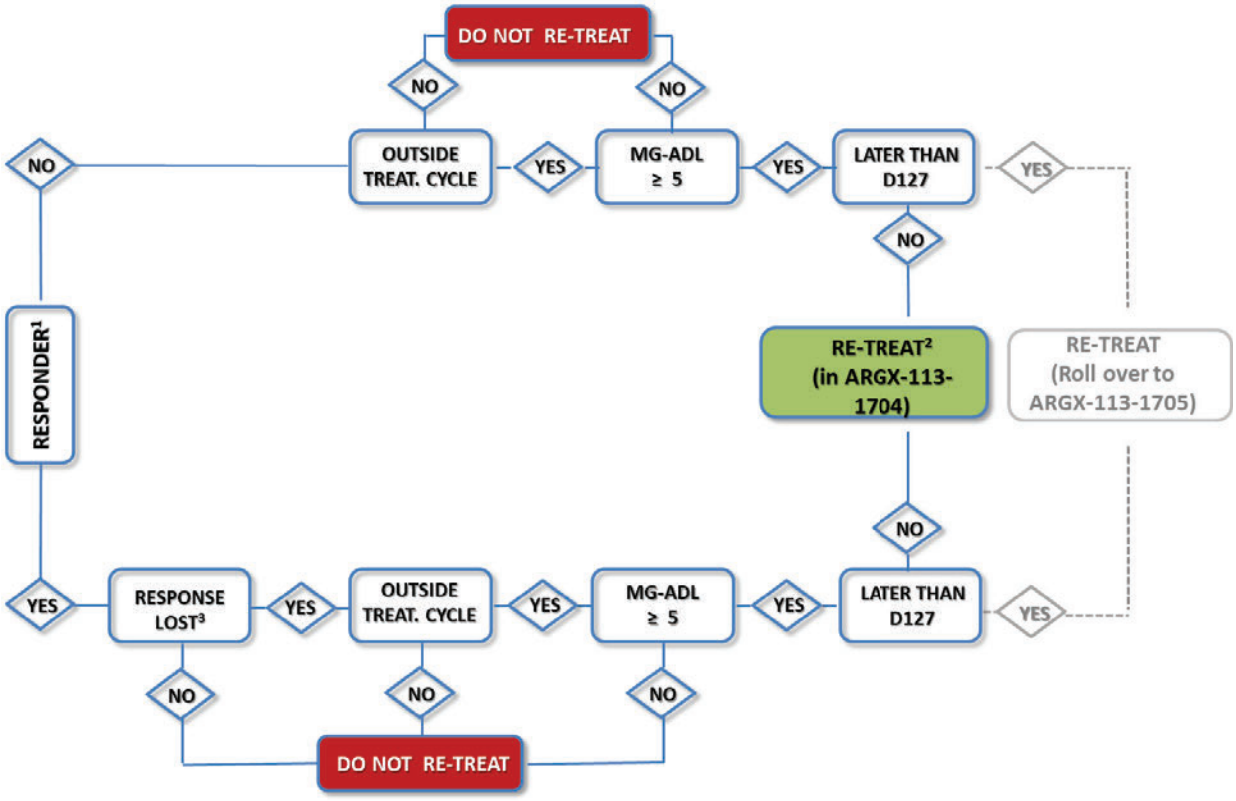
Appendix 6 Laboratory Evaluations

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). Total IgG at Screening only[1]
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.
Serology	Human immunodeficiency virus (HIV) antibodies (1 and 2), Hepatitis B surface antigen (HBsAg), antibodies to the surface and core antigens of the hepatitis B virus (anti-HBs and anti-HBc), hepatitis C virus antibody (HCV-Ab)
Other	Serum and urine human chorionic gonadotrophin (ß-HCG), Follicle-stimulating hormone (FSH) test
Pharmacokinetics (PK)	Concentration levels of ARGX-113
AChR-/MuSK-antibody serotype	AChR-antibody (binding) levels and anti-muscle-specific kinase (MuSK) antibodies (in all patients; at Screening only)[2]
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-MuSK antibodies in MuSK-Ab seropositive patients only
Anti-drug antibodies (ADA)	Levels of anti-ARGX-113 binding and neutralizing antibodies (if applicable)

Note: All blood and urine samples will be collected locally (pre-dose on dosing days) and analyzed centrally.
[1] For eligibility purpose, total IgG will be measured (as part of clinical lab) centrally at Screening. At all other timepoints, total IgG will be analyzed, together with the other PD parameters, by a specialty lab.
[2] In case the AChR-Ab result is not available in time (i.e. within the 2 weeks screening window), the screening window can be enlarged on an ad-hoc base with maximum 5 calendar days.


CCI

Appendix 8 Decision Tree for Re-treatment – Part A

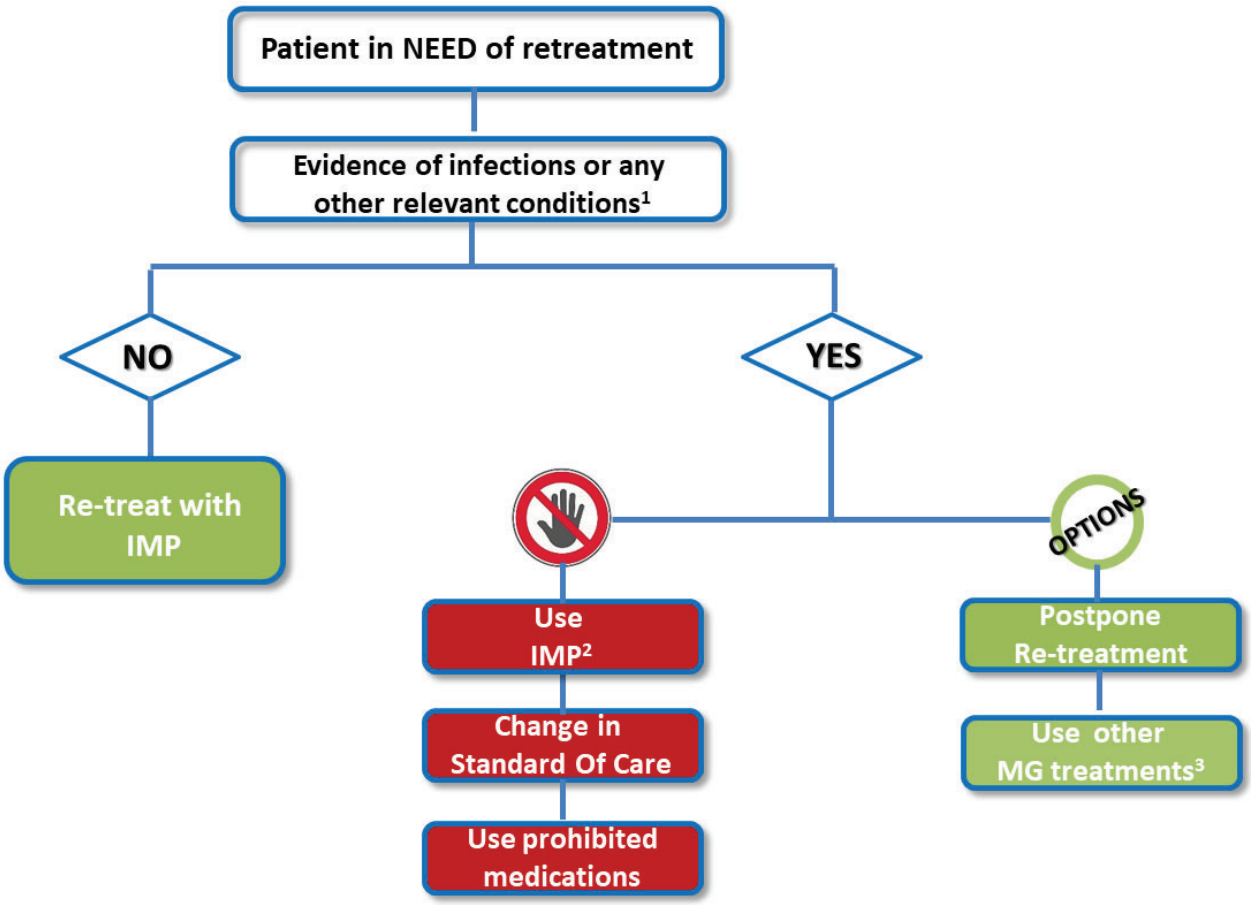


[1] MG-ADL decrease of ≥ 2 points (compared to the corresponding TC baseline) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of IMP of the corresponding cycle.

[2] Retreat at the first timepoint when all re-treatment conditions apply and if no infection or confounding conditions exist (see also section 4.1).

[3] MG-ADL decrease of < 2 compared to corresponding TC baseline.

Appendix 9 Decision Tree for Re-treatment – Part B



[1] Conditions that may interfere with the correct interpretation of the data or put the patient at undue risk.

[2] Re-treatment with IMP may be reconsidered at next time where conditions for re-treatment are met, providing that at least 4 weeks have past after other MG treatment.

[3] Provided that it is not a SoC or a prohibited medication.