Clinical Study Protocol

Protocol Title:	**A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness**
Protocol Number:	**ARGX-113-1602**
Date of Protocol:	**2016-11-28, Version 2.0**
Product:	**ARGX-113**
IND No.:	[redacted]
EudraCT No.:	**2016-002938-73**
Study Phase:	**II**
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24-Hour Urgent Medical Helpline Number: **+1 973 659 6677 (primary number) or**
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Safety Mailbox: **E-mail:** [redacted]

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 and CRO Representatives

PROTOCOL TITLE: **A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness**

PROTOCOL NO: **ARGX-113-1602**

SPONSOR REPRESENTATIVE

	[redacted]	**28 Nov 2016**
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[redacted]	**Signature**	**Date**

Chief Medical Officer, argenx

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PROTOCOL NO: **ARGX-113-1602**

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Medical Director, Quintiles

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Senior Biostatistician, Quintiles

Signature of Investigator

PROTOCOL TITLE: A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness

PROTOCOL NO: ARGX-113-1602

This protocol is a confidential communication of argenx. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the study will be conducted. Return the signed original copy to the local representative of your Sponsor's designated CRO (Quintiles).
A scanned copy of this page should also be e-mailed to [redacted]

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

SYNOPSIS

Name of Sponsor:	argenx
Name of Investigational Medicinal Product:	ARGX-113
Name of Active Ingredient:	A human anti-neonatal Fc receptor IgG1 Fc fragment
Title of Study:	A Randomized, Double-blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of ARGX-113 in Patients with Myasthenia Gravis who have Generalized Muscle Weakness
Protocol No:	ARGX-113-1602
Study sites:	This study will be conducted in up to 25 sites.
Study duration: The study duration for each patient is 13 weeks. It consists of a Screening period of 15 days, a 3 week Treatment period, and an 8 week Follow-up (FU) period.	**Phase:** II

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of ARGX-113.

Secondary Objectives:

- To evaluate the clinical effect of ARGX-113 using:
  - Myasthenia Gravis-Activities of Daily Living (MG-ADL) score.
  - Quantitative-Myasthenia Gravis score (QMG).
  - Myasthenia Gravis Composite score (MGC).
- To evaluate the impact of ARGX-113 on quality of life using 15-item quality of life scale for Myasthenia Gravis (MGQoL15r [revised version]).
- To investigate the pharmacokinetics (PK) of ARGX-113.
- To assess the pharmacodynamic (PD) markers (e.g., total immunoglobulin G (IgG) and subtypes, anti-acetylcholine receptor [AChR] antibodies).
- To evaluate the immunogenicity of ARGX-113.

Methodology: This is a randomized, double-blind, placebo-controlled, multicenter Phase II study to evaluate the safety, efficacy, and pharmacokinetics of ARGX-113 for the treatment of autoimmune Myasthenia Gravis (MG) with generalized muscle weakness.

Approximately 24 patients will be randomized.

The study will include a Screening period of maximum 15 days, a Treatment period of 3 weeks from Visit 1 to Visit 7 and a Follow-Up (FU) period of 8 weeks starting after completion of Visit 7 to Visit 16. Although the FU period is from Visit 8 to Visit 16, the FU in fact starts immediately after the last Investigational Medicinal Product (IMP) infusion at Visit 7.

During the Screening Period, patients' eligibility will be evaluated for study participation.

During the Treatment period, eligible patients will be 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 total dose per IMP infusion is capped at 1200 mg for patients with body weight ≥ 120 kg.
Patients will receive ARGX-113 or placebo according to the following regimen:

- Patients will receive ARGX-113 or matching placebo via intravenous (IV) infusion over a period of 2 hours on Days 1 (Visit 1), 8±1 (Visit 3), 15±1 (Visit 5), and 22±1 (Visit 7).
- The Treatment period consists of 7 visits (of which the 3 visits between the weekly dosing visits are optional).

At the end of the 3 weeks Treatment period, the patient will enter a FU period for 8 weeks.
During the FU period, 9 visits (of which 1 visit is optional) will take place as detailed in Table 1.
Study procedures including endpoint assessments will be performed according to the Schedule of

Assessments as detailed in Table 1. In this study, SoC for a patient is the stable dose and administration of their MG treatment prior to enrollment. Permitted SoC for MG treatment under this protocol include azathioprine (AZA), other non-steroidal immunosuppressant drugs (NSIDs: e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as cholinesterase inhibitors. Patients should be on a stable dose and frequency of SoC prior to enrollment as detailed in of Section 5.3.1 (Criterion 5) that should be maintained throughout the study without any increase or decrease. Patients receiving cholinesterase inhibitors will be required to be on a stable dose for >2 weeks prior to Screening. In addition, cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA][1], prior to performing the MGQoL15r, MG-ADL, QMG, and MGC assessments at Screening, Visits 1, 3, 5, 7, 9, 10, 11, 12, 14, and 16. During the study, no changes in the dose level and frequency of ARGX-113 or the SoC will be allowed. However, if necessary, patients may receive rescue therapy if their MG deteriorates as judged by the Investigator on the basis of parameters such as changes in MGQoL15r, MG-ADL, QMG, MGC on any study day. Rescue therapy will be determined by the Investigator based on an overall clinical assessment. Rescue therapy may include intravenous immunoglobulin (IVIg), plasma exchange (PE), or any other treatment chosen by the Investigator. 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 contract research organization (CRO, Quintiles); where possible prior to actual implementation of the rescue therapy. In case rescue therapy is needed (due to deterioration of MG), patients will be discontinued from treatment with IMP, but will be followed up for safety. Any patient who discontinues study treatment due to safety concerns will be followed up for safety and wherever possible for efficacy. For patients who discontinue the study early, all the procedures listed for Early Discontinuation (ED) visit (same procedures as for the End-of-Study [EoS] visit or Visit 16) in the Schedule of Assessments (Table 1) are to be performed (early discontinuation). This study is exploratory and not powered to address any pre-defined hypothesis. The safety and efficacy analysis will be performed on the safety analysis set, which includes all patients who received at least one infusion of ARGX-113 or placebo.	
Planned number of Patients:	Approximately 36 patients will be screened in order to randomize approximately 24 patients (12 patients per treatment arm) to get at least 20 patients who received at least 3 doses of IMP (either ARGX-113 or placebo) and who completed at least 2 weeks of follow-up post last dose (See Appendix 14.6). Patients may be replaced in certain circumstances (See Section 5.3.6 and Table 2). Final decision for replacement of patients will be done on a case-by-case basis in consultation with the Medical Monitor at the Sponsor's designated contract research organization (CRO, Quintiles) and/or the Medical Director at the Sponsor's end.
Criteria for inclusion and exclusion:	**Inclusion Criteria:** 1. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures (including required study visits). 2. Male or female patients aged ≥18 years. 3. Diagnosis of autoimmune MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III, or IVa, and likely

	not in need of a respirator for the duration of the study as judged by the Investigator. The confirmation of the diagnosis should be documented and supported by: • Positive serologic test for anti-AChR antibodies before Screening and • at least 1 of the following 3 tests: (i) History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation or (ii) History of positive edrophonium chloride test, or (iii) Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors as assessed by the treating physician. 4. A total score of ≥ 5 on the MG-ADL at Screening and Baseline with more than 50% of this score attributed to non-ocular items. 5. Patients are required to be on a stable dose of their MG treatment prior to randomization. For patients receiving AZA, other NSIDs, steroids, and/or cholinesterase inhibitors as concomitant medications the following conditions will apply: • AZA: treatment initiated at least 12 months ago and no dose changes in the last 6 months before Screening. • Other NSIDs (e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide) treatment initiated at least 6 months ago and no dose changes in the last 3 months before Screening. • Steroids treatment initiated at least 3 months prior to and no dose changes in the last month before Screening. • Cholinesterase inhibitors: to be on a stable dose for >2 weeks before Screening. Note: cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA][1], before the MGQoL15r, MG-ADL, QMG, and MGC assessments. 6. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit 1 prior to administration of IMP. Female 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.

	7. Female participants of childbearing potential must agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the study and for 90 days after the discontinuation of the IMP. Adequate contraceptive methods include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, or a female participant who is not of childbearing potential. Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks before Screening. 8. Sterilized male patients who have had vasectomy with documented aspermia post procedure can be included. In addition, male patients must be advised not to donate sperm during this period from signing of Informed Consent Form (ICF), throughout the duration of the study, and for 90 days after the last administration of IMP. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use effective method of double barrier contraception (e.g., condom with spermicidal cream or jelly, 1 hormonal plus 1 barrier method or 2 simultaneous barrier methods). Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. **Exclusion Criteria:** 1. Females who are pregnant or lactating. 2. MGFA Class I, IVb, and V. 3. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening; or history of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or *Mycobacterium tuberculosis*. Patients must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®-TB Gold test at Screening. Patients with an indeterminate QuantiFERON®-TB Gold test result will be allowed one retest; if not negative on retesting, the patient will be excluded. 4. At Screening, have clinically significant laboratory abnormalities or as below: • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN). • Total serum bilirubin of > 1.5 × ULN (except for

	Grade 1 hyperbilirubinemia solely due to a medical diagnosis of Gilbert's syndrome). • Serum creatinine > 1.5 mg/dL and creatinine clearance < 50 ml/min (using the Chronic Kidney Disease Epidemiology [CKD-EPI]-Creatinine formula). • Clinically Significant proteinuria (i.e., > 3 × ULN). • Hemoglobin ≤ 9 g/L. • Thyroid stimulating hormone or thyroglobulin outside of the central laboratory normal range. • International normalized ratio (INR) or activated partial thromboplastin time (aPTT) > 1.2 × ULN. • Total immunoglobulin G level < 6 g/L. 5. Body Mass Index (BMI) at Screening ≥ 35 kg/m^2. 6. Use of rituximab, belimumab, eculizumab or any monoclonal antibody for immunomodulation within 6 months prior to first dosing. Patients with prior exposure to rituximab must have CD19 counts within the normal range per the central laboratory at Screening. 7. Use of any biological therapy or investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening. 8. Immunoglobulins given by IV (IVIg), or intramuscular route, or plasmapheresis/plasma exchange (PE) within 4 weeks before Screening. 9. Have known autoimmune disease other than MG that would interfere with the course and conduct of the study (such as uncontrolled thyroid disease or severe RA). 10. Have received vaccinations within 4 weeks before Screening or have any vaccinations planned during the study. 11. Have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders at any time, unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before Screening. Patients with completely excised non-melanoma skin cancers (such as basal cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time. 12. Have a history of cerebrovascular accident or myocardial infarction within the last 12 months before Screening, or current severe/unstable angina, arrhythmia, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV, or uncontrolled hypertension. 13. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious diseases) which, in the opinion of the Investigator, could confound the results of the study or put the patient at undue risk. 14. Major past surgery (e.g., heart valve replacement, hip replacement) that, in the opinion of the Investigator, poses a risk to patient's safety or interferes with the study evaluation, procedures or completion.

	15. Thymectomy when performed < 3 months prior to Screening. 16. History or presence of alcoholism or drug/chemical/substance abuse within 2 years before Screening per Investigator's opinion.
Test product, dose and mode of administration:	In this study, the Investigational Medicinal Product is ARGX-113 which is a human anti-neonatal Fc receptor IgG1 Fc fragment with immune modulating properties. A dose of 10 mg/kg of body weight of ARGX-113 will be administered as an intravenous (IV) infusion over a period of 2 hours at Visits 1, 3, 5, and 7. 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 but without the active ingredient will be administered intravenously over a period of 2 hours at Visits 1, 3, 5, and 7.

Criteria for evaluation:

Primary Endpoint:

- Evaluate the incidence and severity of adverse events (AEs) and serious AEs (SAEs).
- Evaluate vital signs, electrocardiogram (ECG), and laboratory assessments.

Secondary Endpoints:

- Score change from Baseline (defined as the score immediately prior to first dose at Visit 1) at Visits 3, 5, 7, 9, 10, 11, 12, 14, and 16 for the following:
  - MG-ADL
  - QMG
  - MGC
  - MGQoL15r
- Maximum reduction from Baseline across visit days for MG-ADL, QMG, MGC, and MGQoL15r score.
- Pharmacokinetic parameters of ARGX-113 including maximum observed concentration (C_{max}), time of maximum concentration (t_{max}), concentration prior to dosing (C_{trough}), half-life, ($t_{1/2,\lambda z}$), and accumulation ratio (R_{ac}).
- Evaluation of PD markers: total IgG (and subtypes) and anti-AChR antibodies.
- Evaluate the incidence of anti-drug antibodies (ADA) to ARGX-113.
- Exploratory pharmacogenetic assessments in patients who sign a separate pharmacogenetic ICF to examine FcRn polymorphisms.

Statistical methods: For the primary objective of safety and tolerability, AEs, SAEs, vital signs, ECGs and clinical laboratory assessments at specific time points will be evaluated. All safety data will be summarized descriptively. Baseline will be the last assessment before the first dose of the IMP. Number and percentage of AEs will be presented for each treatment by Preferred Term (PT) and System Organ Class (SOC) of the current Medical Dictionary for Regulatory Authorities (MedDRA) dictionary. Individual listings of all serious AEs and discontinuation from IMP will be summarized using the current MedDRA dictionary.

For the secondary objective of clinical effect, the change from Baseline will be evaluated. Actual and change in data from Baseline will be summarized descriptively for each treatment by visits. For change from Baseline, analysis of covariance (ANCOVA) will be used for continuous variables; (unless otherwise specified) with the terms of treatment as fixed effects and Baseline value as covariate in the model. All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 or with 2-sided 95% confidence intervals (CI). No inferential hypothesis are tested in these secondary variables and summary statistics and CIs for these are not adjusted for multiplicity. The p-value if presented will not be considered for any inference. Analysis of Baseline characteristics will be summarized appropriately via descriptive statistics or visual presentation. For analysis of categorical data, Fisher's exact test, Chi-squared test, or Cochran-Mantel-Haenszel (CMH) test will be performed.

For the secondary objectives for PK, the PK of ARGX-113 will be evaluated by assessment of drug concentrations in plasma. These drug concentrations will be listed and summarized for each sampling time point using arithmetic mean, standard deviation (SD), minimum, median, maximum, number of observations and number of observations ≥lower limit of quantification (LLOQ). The PK parameters except for t_{max} will be summarized using geometric mean (G_{mean}), geometric coefficient of variation (GCV), arithmetic mean, SD, minimum, median, and maximum number of observations. In addition, t_{max} will be summarized using median, minimum, maximum, and number of observations. Observed and change from Baseline in PD, ADA biomarkers will be listed, summarized, and presented graphically as appropriate.

Table 1 Schedule of Assessments

Assessments	Screening[a]	Visits																
		Treatment period (Visit 1 to Visit 7)							*Follow-Up period (Immediately after last Infusion at Visit 7 to Visit 16)*									
Visits	Screening Visit	V1	V2**	V3	V4**	V5	V6**	V7	V8**	V9	V10	V11	V12	V13	V14	V15	V16	
Study Day*		1	5±1	8±1	12±1	15±1	19±1	22±1	26±1	29±1	36±1	43±1	50±1	57±1	64±1	71±1	78±1	Safety Visit
								EoT									*EoS/ED*	*US*
Informed consent[b]	X																	
Inclusion and exclusion criteria	X	X[e]																
Medical/surgical history	X																	
Randomization		X[e]																
Demographic Characteristics	X																	
Physical examination[c] including Height[d] and Weight	X[c, d]	X		X		X		X[c]		X	X	X	X		X		X[c]	X
Vital Signs (Blood Pressure, Heart rate, Oral body temperature)	X	X[e]		X[e]		X[e]		X[e]		X	X	X	X		X		X	X
MGQoL15r[e]	X	X		X		X		X		X	X	X	X		X		X	
MG-ADL[e]	X	X		X		X		X		X	X	X	X		X		X	
QMG[e]	X	X		X		X		X		X	X	X	X		X		X	
MGC[e]	X	X		X		X		X		X	X	X	X		X		X	
Clinical laboratory tests[f]	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Pharmacodynamics: anti-AChR antibodies and Immunoglobulin G and its sub-types[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[h]	X	X[e]						X[e]									X	X
Urinalysis	X	X[e]		X[e]		X[e]		X[e]		X	X	X	X		X		X	X
Pharmacokinetics: Blood		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X	X	X	X	X					
Anti-drug antibodies		X[e]				X[e]		X[e]		X	X	X	X		X		X	
Serum Pregnancy test[j]	X																	
Urine Pregnancy test[k]		X		X		X		X				X					X	X
Viral and bacterial tests[l]	X																	
Pharmacogenetics[m]		X		X[m]														
Administration of ARGX-113 or placebo[n]		X		X		X		X										
Suicidality assessment[o]	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Concomitant therapies[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = Body Mass Index; ECG = Electrocardiogram; 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 score; MGC = Myasthenia Gravis Composite score; MGQoL15r = 15-item quality of life scale for Myasthenia Gravis [Revised version]; US = Unscheduled; V = Visit.

*: The allowed window period between visits in Treatment period and Follow-up period is ±1 day provided that 2 consecutive visits are 3 days apart at a minimum. Every effort should be made to schedule every visit on the exact Day (which is relative to the Baseline visit or [Visit 1]) as described in above Schedule of Assessments (Table 1) without the window.

**: The Visits 2, 4, 6, and 8 are optional.

a. To take place within 15 days prior to first administration of the Investigational Medicinal Product (IMP) at Visit 1.
b. No study-related assessment is to be carried out before the patient has signed informed consent.
c. A complete physical examination will be performed at Screening, Visit 7, and at Visit 16/EoS/ED. An abbreviated examination will be done at all other visits. On dosing days, physical examination including weight measurement should be performed pre-dose.
d. Height should only be measured at Screening (and Body Mass Index [BMI] to be calculated accordingly at Screening only).
e. Randomization to be performed only after confirmation of eligibility of the patient including the MG-ADL score assessed at Visit 1 and prior to dosing at Visit 1. The assessments for vital signs, urinalysis, and anti-drug antibodies, must be performed pre-dose at visits when the Investigational Medicinal Product (IMP) is administered (Visits 1, 3, 5, and 7). **Efficacy assessments** scheduled on designated Days should be completed pre-dose on each dosing day and **should be performed prior to any other study specific assessment**, except for obtaining informed consent at Screening. **Efficacy assessments** should be performed **in the following sequence** (at each study visit including these assessments): **MGQoL15r, MG ADL, QMG, and MGC**. Cholinesterase inhibitors must be held for at least 12 hours before the MGQoL15r, MG-ADL, QMG, and MGC assessments (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA])[1]. A total score ≥5 on the MG-ADL with more than 50% of this score attributed to non-ocular items should be met at both Screening and Baseline (Visit 1) to confirm eligibility.
f. Sampling for clinical laboratory tests is to be performed pre-dose on dosing days and tests will include hematology (hemoglobin, platelet count, white blood cell count with differential); blood chemistry (including creatinine, creatinine clearance, blood urea nitrogen [BUN], glucose, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, gamma-glutamyl transferase [GGT], C-reactive protein [CRP], alkaline phosphatase [AP], lactate dehydrogenase [LDH], uric acid, albumin, potassium, calcium, sodium, thyroglobulin, International normalized ratio or activated partial thromboplastin time [aPTT], CD19 counts). Patients need to be fasting for at least 8 hours prior to this sampling.
g. Sampling for pharmacodynamic biomarkers is to be performed pre-dose on dosing days and include anti-AChR antibodies and immunoglobulin G and its sub-types. Analysis of anti-AChR antibodies will include anti-AChR binding antibodies and anti-AChR blocking antibodies. IgG measurements include total IgG, IgG subtypes (IgG 1, IgG 2, IgG 3, and IgG 4). In addition, IgA, IgD, IgE, and IgM will also be assessed.
h. ECG (heart rate, PR, QT, and QRS interval) will be read locally and should be performed pre-dose on dosing days.
i. Pharmacokinetic (PK) assessments should be done both pre- and post-dose (within 30 minutes prior to start of infusion for pre-dose sample and within 30 minutes after end of infusion for post-dose sample) on all IMP infusion days.
j. Serum pregnancy test must be performed in women of childbearing potential at Screening from the blood sample collected for clinical laboratory tests at the central laboratory.
k. Urine pregnancy test will be performed locally pre-dose at Visits 1, 3, 5, 7, 11, and 16/EoS/ED.
l. Tests to assess HbsAg, anti-HCV antibodies, Follicle stimulating hormone (FSH), HIV antibodies and tuberculosis serology (QuantiFERON®-TB Gold) test will be performed at the central laboratory.

m. A blood sample for the optional pharmacogenetic testing is to be collected before the first dose of the Investigational Medicinal Product is administered at Visit 1 (Baseline) after a separate pharmacogenetic ICF has been signed, and will be stored for pharmacogenetic analysis. Only if the blood sample at Visit 1 is missed, the sample should be drawn at Visit 3 before the administration of the Investigational Medicinal Product.
n. The Investigational Medicinal Product or placebo will be administered as an IV infusion over a period of 2 hours at Visits 1, 3, 5, and 7. Patients should remain at the site for at least 2 hours following the end of the infusion for safety monitoring based on the patient's clinical status.
o. Suicidal ideation and behavior will be assessed via a targeted question based on the Patient Health Questionnaire item 9 (PHQ-9)[2] at each scheduled visit except the optional visit.
p. Adverse events and intake of concomitant medication(s) will be monitored continuously from signing of informed consent until the last study-related activity at Visit 16. In case of early discontinuation, any AEs/SAEs should be assessed for 30 days following the early discontinuation visit and until satisfactory resolution or stabilization.

TABLE OF CONTENTS

LIST OF INTEXT TABLES

LIST OF FIGURES

1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACh	Acetylcholine
AChE	Anticholinesterase inhibitors
AChR	Acetylcholine receptor
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZA	Azathioprine
b.w.	Body weight
BMI	Body Mass Index
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
C_{trough}	Concentration observed prior to dosing
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EoS	End-of-Study
EoT	End-of-Treatment
FAS	Full analysis set
Fc	Fragment, crystallized
FcRn	Neonatal Fc receptor
FU	Follow-Up
GCP	Good Clinical Practice
GCV	Geometric coefficient of variation
GGT	Gamma-glutamyl transferase
G_{mean}	Geometric mean
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IA	Immunoadsorption

ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
IVIg	Intravenous immunoglobulin
IxRS	Interactive Voice/Web response system
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory authorities
MG	Myasthenia Gravis
MG-ADL	Myasthenia Gravis activities of daily living
MGC	Myasthenia Gravis composite score
MGFA	Myasthenia Gravis Foundation of America
MG-QOL	Myasthenia Gravis Quality of Life scale
MGQoL15r	15-item Quality of life scale for Myasthenia Gravis [revised version]
NOAEL	No Observed Adverse Effect Levels
NSID	Non-steroidal immunosuppressant drugs
PD	Pharmacodynamics
PE	Plasma exchange
pH	Potential of hydrogen or concentration of hydrogen ions
PHQ-9	Patient Health Questionnaire item 9
PK	Pharmacokinetics
PR interval	Duration from the start of the T wave to the start of the QRS complex, representing the time taken for electrical activation (of the cardiac conduction system) to pass from the sinus node to the atrium, the atrioventricular node and the His-Purkinje system to the ventricle
PT	Preferred term
q4d	Administered every 4 days
q7d	Administered every 7 days
QMG	Quantitative Myasthenia Gravis score
QRS interval	Pertains to depolarization of ventricles

QT interval	Duration from the start of QRS interval to the end of the T wave, representing the time taken for depolarization and repolarization of the ventricular myocardium
R_{ac}	Accumulation ratio
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SoC	Standard of care
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2,\lambda z}$	Apparent terminal half-life
t_{max}	The time of occurrence of C_{max}
ULN	Upper limits of normal
US	United States
WHO-DD	World Health Organization drug dictionary

2.0 INTRODUCTION

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.[3]

2.1 Background Information

Antibodies, especially IgG, play a predominant role in the pathogenesis and the treatment of many autoimmune diseases such as MG. In most cases, MG is characterized by antibody responses to neuromuscular junction proteins such as skeletal muscle AChR. High-affinity, anti-AChR antibodies bind to the muscle endplate leading to AChR dysfunction or loss via activation of complement, cross-linking of AChR receptors, or direct blockade of acetylcholine (Ach) binding sites, thereby leading to an impaired signal transduction and resulting muscle weakness.[4, 5] The disease is typically managed with acetylcholinesterase inhibitors and immunosuppressive medications. Acute exacerbations are treated using either therapeutic plasma exchange (PE), immunoadsorption (IA) or intravenous immunoglobulin (IVIg). These therapeutic options, except acetylcholinesterase inhibitors, aim at reducing the levels of pathogenic autoantibodies but suffer from severe side effects and/or comorbidities.[6]

In order to treat IgG-mediated autoimmunity, it would be beneficial to lower levels of pathogenic autoantibodies rapidly and sustainably. Antagonizing the neonatal Fc receptor (FcRn) could be a therapeutic approach to achieve this as FcRn is a multifunctional molecule primarily involved in IgG transport and homeostasis, that influences immunoglobulin G (IgG) serum levels and tissue distribution at all stages of life.[7, 8]. Following IgG uptake by pinocytosis, the Fc part of IgGs binds FcRn with high affinity in early, acidic endosomes with pH <6.5. Through its ability to rescue IgG from destruction in the lysosomal compartment, FcRn is responsible for the maintenance of high concentrations of IgG in circulation and concomitantly for the long half-life of IgG compared to other Ig isotypes. 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.

2.2 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)[9] 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 endogenous 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™)[10, 11]

In murine *in vivo* disease models for rheumatoid arthritis and multiple sclerosis a clear improvement in disease score was observed after treatment with an ABDEG™-equipped molecule. This improvement was accompanied with systemic lowering of autoantibody levels.

Pharmacokinetic and PD studies in cynomolgus monkey confirmed the antibody-clearing properties of ARGX-113 in a relevant animal model. A single infusion of ARGX-113 resulted in a decrease of endogenous IgG up to 55% without altering serum albumin concentrations as well as IgM or IgA levels. This PD effect was proven to be more potent than IVIg, which is considered a standard of care therapy in MG, both in rapidity of onset as in depth of the PD effect. Repeated dosing could improve the PD effect up to a maximum IgG reduction of 75%.

These pre-clinical data validated the further development of ARGX-113 for assessing its therapeutic potential in IgG-driven autoimmune indications.

To this end, a Phase I dose-escalation study in healthy volunteers was initiated. In this study ARGX-113 was administered to healthy volunteers in single doses (up to 50 mg/kg) as well as multiple doses (up to 25 mg/kg). ARGX-113 was proven to be safe and tolerable in this healthy volunteer study and pre-clinical PD parameters could be confirmed in a human setting.

The proposed Phase II study aims to further establish the safety, efficacy, PK and PD of ARGX-113 in a patient setting, namely in patients with autoimmune MG with generalized muscle weakness, and thereby validating the concept of autoantibody reduction as a therapeutic treatment modality in this indication.

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

2.3 Rationale and Standard of Care

The mainstays of MG treatment are AChE inhibitors, immunosuppressants and immunomodulating therapies. In the mild form of the disease, AChE inhibitors are used initially. These agents include pyridostigmine, neostigmine, and edrophonium and their effectiveness varies widely. Patients with generalized MG are treated with corticosteroids. Unfortunately, corticosteroids 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. Other non-steroidal immunosuppressive (NSIDs) agents are commonly used and include azathioprine (AZA), mycophenolate mofetil, cyclosporine, cyclophosphamide, and rituximab. However, the effectiveness of many of these medications varies widely among patients, take a long time to take effect and have numerous adverse consequences.[12]

Plasma exchange (PE), immunoadsorption and IVIg are used for short-term treatment of MG exacerbations and when it is desirable to achieve a rapid clinical response. Plasma exchange temporarily reduces the concentrations of circulating anti-AChR antibodies and in most patients produces improvement in a matter of days. 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 common side-effects such as hypotension, paresthesia, infections, and thrombotic complications. IVIg is widely used for patients with exacerbating MG and data from randomized controlled studies show efficacy similar to PE. The mechanisms by which IVIg produce improvement are not clear, but two important possibilities are competition with autoantibodies (i.e., FcRn binding) and Fc receptor binding. It is important to note that a higher degree of auto-antibody reduction, faster onset and better clinical efficacy has been observed for PE and immunoadsorption when compared with IVIg. A fast onset is important for treatment of patients experiencing exacerbations.[13, 14]

In preclinical studies, ARGX-113 demonstrated high potency and rapid onset of action in IgG autoantibody reduction. In murine *in vivo* disease models, ARGX-113 demonstrated a high therapeutic potential linked to a rapid clearance of IgG autoantibodies. Studies in cynomolgus monkeys confirmed this rapid onset of IgG reduction, and demonstrated specificity of this effect as IgA, IgM, and albumin levels were not affected.

In addition, following administration of a single dose of 10 mg/kg in healthy volunteers there was a 55% decrease of serum IgG levels. Six doses of 10 mg/kg administered every four days were considered safe, well tolerated and resulted in a maximum effect on serum IgG decrease.

Myasthenia gravis is considered to be a highly autoantibody driven disease. ARGX-113 is postulated to be a highly specific targeted therapy to reduce the autoantibody levels. Results from the Phase I study indicate it is safe and tolerable based on data from healthy volunteers. Therefore, ARGX-113 is believed to be a promising treatment to reduce autoantibodies in MG patients.

2.4 Risk Assessment

Both a single and a repeat dose toxicology study consistent with Good Laboratory Practice (GLP) were performed.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety and tolerability of ARGX-113.

3.2 Secondary Objectives

- To evaluate the clinical effect of ARGX-113 using:
    - Myasthenia Gravis-Activities of Daily Living (MG-ADL) score
    - Quantitative-Myasthenia Gravis score (QMG)
    - Myasthenia Gravis Composite score (MGC).
- To evaluate the impact of ARGX-113 on quality of life using 15-item quality of life scale for Myasthenia Gravis (MGQoL15r [revised version]).
- To investigate the PK of ARGX-113.
- To assess PD markers (e.g., total immunoglobulin G (IgG) and subtypes, anti-AChR antibodies).
- To evaluate the immunogenicity of ARGX-113.

4.0 SAFETY, EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ENDPOINTS

4.1 Primary Endpoint

- Evaluate the incidence and severity of adverse events (AEs) and serious AEs (SAEs).
- Evaluate vital signs, ECG, and laboratory assessments.

4.2 Secondary Endpoints

- Score change from Baseline (defined as the score immediately prior to first dose at Visit 1) at Visits 3, 5, 7, 9, 10, 11, 12, 14, and 16 for the following:
    - MG-ADL
    - QMG
    - MGC
    - MGQoL15r
- Maximum reduction from Baseline across visit days for MG-ADL, QMG, MGC, and MGQoL15r score.
- Pharmacokinetic parameters of ARGX-113 including maximum observed concentration (C_{max}), time of maximum concentration (t_{max}), concentration prior to dosing (C_{trough}), half-life ($t_{1/2,\lambda z}$), and accumulation ratio (R_{ac}).
- Evaluation of PD markers: total IgG (and subtypes) and anti-AChR antibodies.
- Evaluate the incidence of anti-drug antibodies (ADA) to ARGX-113.
- Exploratory pharmacogenetic assessments in patients who sign a separate pharmacogenetic ICF to examine FcRn polymorphisms.

5.0 INVESTIGATIONAL PLAN

5.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled multicenter Phase II study to evaluate the safety, efficacy, and pharmacokinetics (PK) of ARGX-113 for the treatment of autoimmune MG with generalized muscle weakness.

Approximately 24 patients will be randomized.

The study will include a Screening period of maximum 15 days, a Treatment period of 3 weeks from Visit 1 to Visit 7 and a Follow-Up (FU) period of 8 weeks starting after completion of Visit 7 to Visit 16. Although the FU period is from Visit 8 to Visit 16, the FU in fact starts immediately after the last Investigational Medicinal Product (IMP) infusion at Visit 7.

During the Screening Period, patients' eligibility will be evaluated for study participation.

During the Treatment period, eligible patients will be 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 total dose per IMP infusion is capped at 1200 mg for patients with body weight ≥ 120 kg.

Patients will receive ARGX-113 or placebo according to the following regimen:

- Patient will receive ARGX-113 or matching placebo via intravenous (IV) infusion over a period of 2 hours on Days 1 (Visit 1), 8±1 (Visit 3), 15±1 (Visit 5), and 22±1 (Visit 7).
- The Treatment period consists of 7 visits (of which the 3 visits between the weekly dosing visits are optional).

At the end of the 3 weeks Treatment period, the patient will enter a FU period for 8 weeks.

During the Follow-Up period, 9 visits (of which 1 visit is optional) will take place as detailed in Table 1.

Study procedures including endpoint assessments will be performed according to the Schedule of Assessments as detailed in Table 1.

In this study, SoC for a patient is the stable dose and administration of their MG treatment prior to enrollment. Permitted SoC for MG treatment under this protocol include azathioprine

(AZA), other non-steroidal immunosuppressant drugs (NSIDs: e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as cholinesterase inhibitors. Patients should be on a stable dose and frequency of SoC prior to enrollment as detailed in of Section 5.3.1 (Criterion 5) that should be maintained throughout the study without any increase or decrease.

Patients receiving cholinesterase inhibitors will be required to be on a stable dose for >2 weeks prior to Screening. In addition, cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA][1], prior to performing the MGQoL15r, MG-ADL, QMG, and MGC assessments at Screening, Visits 1, 3, 5, 7, 9, 10, 11, 12, 14, and 16.

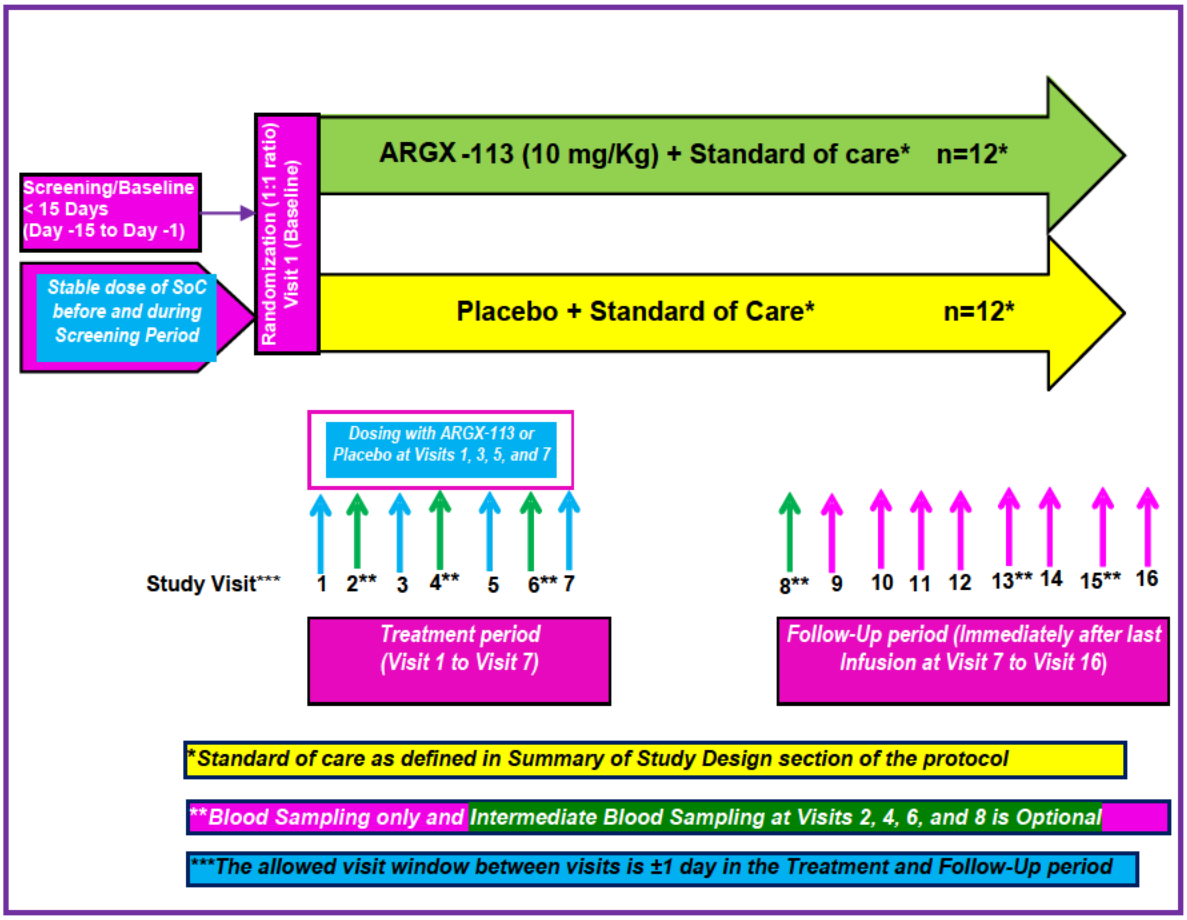
During the study, no changes in the dose level and frequency of ARGX-113 or the SoC will be allowed. However, if necessary, patients may receive rescue therapy if their MG deteriorates as judged by the Investigator on the basis of parameters such as changes in MGQoL15r, MG-ADL, QMG, MGC on any study day.

Rescue therapy will be determined by the Investigator based on an overall clinical assessment. Rescue therapy may include IVIg, PE, or any other treatment chosen by the Investigator. 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 Sponsor's designated contract research organization (CRO, Quintiles); where possible prior to actual implementation of the rescue therapy. In case rescue therapy is needed (due to deterioration of MG), patients need to be discontinued from the treatment, but will be followed up for safety. Any patient who discontinues study treatment due to safety concerns will be followed up for safety and wherever possible for efficacy.

For patients who discontinue the study early, all the procedures listed for the Early Discontinuation (ED) visit (same procedures as for the End-of-Study [EoS] visit or Visit 16) in the Schedule of Assessments (Table 1) are to be performed (early discontinuation). This study is exploratory and not powered to address any pre-defined hypothesis. The safety and efficacy analysis will be performed on the safety analysis set, which includes all patients who received at least one infusion of ARGX-113 or placebo.

A schematic of study design is presented in Figure 1.

Figure 1 Schematic of Study Design for Protocol ARGX-113-1602



Abbreviations: ARGX = Investigational Medicinal Product; n = sample size; SoC = Standard of Care.

5.2 Discussion of Study Design

ARGX-113, a novel immunomodulator, has been found to be safe and well tolerated in non-clinical studies and a single and multiple dose Phase I study. The safety and tolerability assessments in the Phase I study was judged sufficient to fulfill the primary objective of this study. Preliminary evidence suggests that ARGX-113 has shown promising effect with decreased serum IgG levels. This effect has been well characterized in pre-clinical studies and justifies its further development in patients with IgG driven autoimmune diseases such as MG.

In the current study, ARGX-113 will be administered for the first time in patients with MG who have generalized muscle weakness, with the aim to evaluate the safety, efficacy, and PK-PD of ARGX-113. This study is designed as a randomized, double-blind, and placebo controlled study to distinguish the effect of the IMP from other influences such as placebo effect or biased observation. Patients will continue to receive their routine SoC during the study irrespective of the treatment they receive because of randomization. Furthermore, patients randomized to ARGX-113 will receive the IMP as an add-on therapy to the routine SoC. Since patients with autoimmune MG eligible for this study continue to have significant residual symptoms that affect their quality of life whilst on SoC, this study offers an opportunity to receive ARGX-113 (a potential new treatment for MG) that may offer additional benefit on top of their routine SoC. It serves as a rational therapeutic approach for IgG mediated immune diseases such as MG by targeting the FcRn-IgG interaction and alleviating autoimmunity by rapidly clearing pathogenic autoantibodies.

The efficacy of ARGX-113 versus placebo will be explored using clinical activity tools commonly used in MG clinical research and clinical practice. Patients achieving clinically meaningful response by studying change from Baseline will be used to explore efficacy data in the current study. All efficacy and safety assessments used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant.

5.3 Selection of Study Population

5.3.1 Inclusion Criteria

Patients will be enrolled in this study only if they meet all of the following criteria:

1. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study protocol procedures (including required study visits).

2. Male or female patients aged ≥18 years.

3. Diagnosis of autoimmune MG with generalized muscle weakness meeting the clinical criteria for diagnosis of MG as defined by the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II, III, or IVa, and likely not in need of a respirator for the duration of the study as judged by the Investigator.

   The confirmation of the diagnosis should be documented and supported by:

   - Positive serologic test for anti-AChR antibodies before Screening and
   - At least 1 of the following 3 tests:

   (i) History of abnormal neuromuscular transmission test demonstrated by single-fiber electromyography or repetitive nerve stimulation or

   (ii) History of positive edrophonium chloride test, or

   (iii) Patient has demonstrated improvement in MG signs on oral cholinesterase inhibitors as assessed by the treating physician.

4. A total score of ≥ 5 on the MG-ADL at Screening and Baseline with more than 50% of this score attributed to non-ocular items.

5. Patients are required to be on a stable dose of their MG treatment prior to randomization. For patients receiving AZA, other NSIDs, steroids, and/or cholinesterase inhibitors as concomitant medications the following conditions will apply:

   - AZA: treatment initiated at least 12 months ago and no dose changes in the last 6 months before Screening.
   - Other NSIDs (e.g., methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide): treatment initiated at least 6 months ago and no dose changes in the last 3 months before Screening.
   - Steroids: treatment initiated at least 3 months prior to and no dose changes in the last month before Screening.
   - Cholinesterase inhibitors: to be on a stable dose for >2 weeks before Screening.

     Note: cholinesterase inhibitors must be held for at least 12 hours consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis

Foundation of America Inc [MGFA][1], before the MGQoL15r, MG-ADL, QMG, and MGC assessments.

6. Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Visit 1 prior to administration of IMP. Female 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.

7. Female participants of childbearing potential must agree to use a highly effective method of contraception (i.e., pregnancy rate of less than 1% per year) during the study and for 90 days after the discontinuation of the Investigational Medicinal Product (IMP). Adequate contraceptive methods include combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, or a female participant who is not of childbearing potential. Female participants and female partners of male study participants using a hormonal contraceptive must also use a barrier method (i.e., condom or occlusive cap [diaphragm or cervical/vault caps]) and should have been stable on their hormonal contraceptive treatment for at least 4 weeks before Screening.

8. Sterilized male patients who have had vasectomy with documented aspermia post procedure can be included. In addition, male patients must be advised not to donate sperm during this period from signing of Informed Consent Form (ICF), throughout the duration of the study, and for 90 days after the last administration of IMP. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use effective method of double barrier contraception (e.g., condom with spermicidal cream or jelly, 1 hormonal plus 1 barrier method or 2 simultaneous barrier methods). Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included.

5.3.2 Exclusion Criteria

Patients will not be enrolled in this study if they meet any of the following criteria:

1. Females who are pregnant or lactating.
2. MGFA Class I, IVb, and V.
3. Have an active infection, a recent serious infection (i.e., requiring injectable antimicrobial therapy or hospitalization) within the 8 weeks prior to Screening; or history of or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or *Mycobacterium tuberculosis*. Patients must have negative test results for HBV surface antigen, HBV core antibody, HCV antibody, HIV 1 and 2 antibodies, and a negative QuantiFERON®-TB Gold test at Screening. Patients with an indeterminate QuantiFERON®-TB Gold result will be allowed one retest; if not negative on retesting, the patient will be excluded.
4. At Screening, have clinically significant laboratory abnormalities or as below:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN).
    - Total serum bilirubin of > 1.5 × ULN (except for Grade 1 hyperbilirubinemia solely due to a medical diagnosis of Gilbert's syndrome).
    - Serum creatinine > 1.5 mg/dL and creatinine clearance < 50 ml/min (using the Chronic Kidney Disease Epidemiology [CKD-EPI]-Creatinine formula).
    - Clinically significant proteinuria (i.e., > 3 × ULN)
    - Hemoglobin ≤ 9 g/L
    - Thyroid stimulating hormone or thyroglobulin outside of the central laboratory normal range.
    - International normalized ratio (INR) or activated partial thromboplastin time (aPTT) > 1.2 × ULN.
    - Total immunoglobulin G level < 6 g/L.
5. Body Mass Index (BMI) at Screening ≥ 35 kg/m^2.
6. Use of rituximab, belimumab, eculizumab or any monoclonal antibody for immunomodulation within 6 months prior to first dosing. Patients with prior exposure to

rituximab must have CD19 counts within the normal range per the central laboratory at Screening.

7. Use of any biological therapy or investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) before Screening.
8. Immunoglobulins given by IV (IVIg), or intramuscular route, or plasmapheresis/plasma exchange (PE) within 4 weeks before Screening.
9. Have known autoimmune disease other than MG that would interfere with the course and conduct of the study (such as uncontrolled thyroid disease or severe RA).
10. Have received vaccinations within 4 weeks before Screening or have any vaccinations planned during the study.
11. Have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders at any time, unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before Screening. Patients with completely excised non-melanoma skin cancers (such as basal cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time.
12. Have a history of cerebrovascular accident or myocardial infarction within the last 12 months before Screening, or current severe/unstable angina, arrhythmia, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV, or uncontrolled hypertension.
13. Have clinical evidence of significant unstable or uncontrolled acute or chronic diseases (i.e., cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious diseases) which, in the opinion of the Investigator, could confound the results of the study or put the patient at undue risk.
14. Major past surgery (e.g., heart valve replacement, hip replacement) that, in the opinion of the Investigator, poses a risk to patient's safety or interferes with the study evaluation, procedures or completion.
15. Thymectomy when performed < 3 months prior to Screening.
16. History or presence of alcoholism or drug/chemical/substance abuse within 2 years before Screening per Investigator's opinion.

5.3.3 Patient Withdrawal from Study

Patient withdrawal in this study only refers to patients withdrawn due to withdrawal of consent. Any other circumstances for early dropout of a patient from the study treatment or study will be referred to as early discontinuation (see Section 5.3.4).

All patients are free to withdraw consent from participation in the study 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 Visit 16/EoS/ED visit in the Schedule of assessments (Table 1).

5.3.4 Early Discontinuation from the Study Treatment or Study

The criteria for enrollment and randomization are to be followed explicitly. If it is noted that a patient who does not meet the inclusion and exclusion criteria is inadvertently randomized and dosed, the Medical Monitor at Sponsor's designated CRO (Quintiles) and the Sponsor's Medical Director must be contacted immediately for discussion on how to proceed with the patient. The patient should be discontinued from the study if there is any compelling safety concern for the patient to continue. The various scenarios that may occur leading to discontinuation of the patient from study and/or treatment is detailed in Table 2.

Table 2 Potential Scenarios for Early Discontinuation from Study and Treatment

Scenario	Discontinuation from Study Treatment	Discontinuation from Study	Replacement if necessary
Safety Concern during Treatment period: In case of a safety concern ***during Treatment period***, Medical Monitor should be consulted and the safety and efficacy assessments per Follow-up period of Table 1 (Visit 9 to Visit 16) must be completed wherever possible.	Discontinue patient from Study Treatment.	Patient does not need to be discontinued from the study depending on the severity and nature of safety event but discontinuation from the study needs to be discussed with the Medical Monitor and/or Sponsor's Medical Director. Wherever possible and appropriate/safe, the patient should continue the schedule of assessments for the Follow-up Period of Table 1 (Visit 9 to Visit 16).	Patients will be analyzed as part of Safety and Efficacy analysis and such a patient will not be replaced.
Safety Concern after Treatment period: In case of a safety concern ***after Treatment period***, the safety and efficacy assessments per Follow-up period of Table 1 (Visit 9 to Visit 16) must be completed where possible and Medical Monitor should be consulted.	Not Applicable.	Patient does not need to be discontinued from the study depending on the severity and nature of safety event but discontinuation from the study needs to be discussed with the Medical Monitor and/or Sponsor's Medical Director. Wherever possible and appropriate/safe, the patient should continue the schedule of assessments in the Follow-up Period of Table 1 (Visit 9 to Visit 16).	Patients will be analyzed as part of Safety and Efficacy analysis and such a patient will not be replaced.
Disease deterioration during Treatment period	After consultation with the Medical Monitor, discontinue patient from Study Treatment, initiate rescue therapy and follow-up for 30 days after the early discontinuation visit or until satisfactory resolution/ stabilization.	After consultation with Medical Monitor and prior to start on rescue therapy, all Visit 16 assessments should be completed. Patients will be discontinued from the study and followed up for safety for an additional 30 days or until satisfactory resolution/stabilization.	Patients will be analyzed as part of Safety and Efficacy analysis and such a patient will not be replaced
Disease deterioration after Treatment period: In case of disease deterioration ***after Treatment period***, the safety and efficacy assessments per Follow-up period of Table 1 (Visit 16) must be completed along with a follow-up for 30 days after the early discontinuation visit or until satisfactory resolution/ stabilization where possible and Medical Monitor should be consulted.	Not Applicable.	Patient's study continuation must be assessed by the Investigator, discussed with the Medical Monitor and/or Sponsor's Medical Director based on clinical examination. Possible examples of worsening include: • Severe deterioration where it may not be possible for patient to continue in the study. • The "End of Treatment Effect" whereby the patient's condition is worsening after any initial improvement while on the study. Prior to initiating rescue therapy, all Visit 16 assessments should be completed and patient should be followed up for safety for an additional 30 days or until satisfactory resolution/ stabilization.	Patients will be analyzed as part of Safety and Efficacy analysis and such a patient will not be replaced

Scenario	Discontinuation from Study Treatment	Discontinuation from Study	Replacement if necessary
Voluntary Discontinuation from IMP or Major Protocol Deviation(s) possibly leading to (Details in a separate Manual) discontinuation from IMP during Treatment period: The Schedule of Assessments for dosing and safety and efficacy evaluations per Table 1 must be performed whenever possible and must be discussed with the Medical Monitor on a case-by-case basis.	In case of voluntary discontinuation during Treatment period or any major protocol deviation(s) possibly leading to discontinuation from IMP during treatment period, a patient should be discontinued from the study treatment.	Patient does not need to be discontinued from the study but discontinuation from the study needs to be discussed with the Medical Monitor and/or Sponsor's Medical Director. And wherever appropriate, patient should continue the schedule of assessments.	Patient will not be replaced if he/she receives at least 3 infusions and completes the Follow-up assessments as indicated in Table 1 with at least 2 weeks of Follow-up post last dose. Patient may be replaced if he/she receives less than 3 infusions and/or ***cannot complete*** at least 2 weeks of Follow-up post last dose as indicated in Table 1.
Major Protocol Deviation(s) (Details in a separate Manual) after Treatment period: The safety and efficacy assessments per Follow-up period of Table 1 (Visit 8 to Visit 16) must be completed where possible and Medical Monitor should be consulted.	Not Applicable.	Patient does not need to be discontinued from the study but discontinuation from the study needs to be discussed with the Medical Monitor and/or Sponsor's Medical Director. Wherever appropriate, patient should continue the schedule of assessments.	Such patients may only be replaced they ***cannot complete*** at least 2 weeks of Follow-up post last dose as indicated in Table 1.

During the study, in case of situations that occur apart from the scenarios described above, the decision to replace patients must be made on a case-by-case basis in consultation with the Medical Monitor at the Sponsor's designated contract research organization (CRO, Quintiles) and/or the Medical Director at the Sponsor's end.

In addition, patients must be discontinued early from the study in the following circumstances:

- Pregnancy.
- Lack of efficacy as judged by the Investigator.
- Emergency unblinding.
- Physician decision.
- Lost to follow up.
- On request of the Sponsor.

For patients who discontinue the study early, all the procedures as those listed for the Early Discontinuation (ED) visit (same procedures as for the End-of-Study [EoS] visit or Visit 16) in the Schedule of Assessments (Table 1) are to be performed (early discontinuation visit).

5.3.5 Follow-Up after Early Discontinuation Visit

Following the early discontinuation visit, any AEs/SAEs should be assessed for 30 days until satisfactory resolution or stabilization.

5.3.6 Replacement of Patients

Patients will not be considered for replacement if they receive a minimum of 3 out of 4 doses of the IMP during the Treatment period and are followed up for at least two weeks in the Follow-up period. Patients who receive fewer than 3 doses of IMP (for reasons other than safety or disease deterioration) and/or cannot complete 2 weeks follow-up post last dose will be considered for replacement. Details on when replacement may be allowed is present in Table 2 (Section 5.3.4).

Replacement of patients will be done on a case-by-case basis in consultation with the Medical Monitor at the Sponsor's designated contract research organization (CRO, Quintiles) and/or the Medical Director at the Sponsor's end and is guided by the scenarios listed in Table 2.

5.3.7 Protocol Deviations/Violations

A protocol deviation is any change, divergence, or departure from the study design or procedure that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment, and that may or will have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Information regarding definition and classification of protocol deviation is detailed in the Protocol Deviation guidance document.

All deviations from the approved protocol must be documented and notified to the Sponsor/Sponsor's designated CRO (Quintiles) at the earliest. The Investigator should not deviate from the protocol, except for patient safety reasons, in which case the deviation must be reported to the Sponsor/Sponsor's designated CRO (Quintiles) immediately. The Sponsor will not assume any resulting responsibility or liability from unapproved deviations. The Investigator, according to applicable regulations and the Ethics Committee's established procedures, will inform the Ethics Committee of protocol deviations.

All instances where the requirements of the study protocol are not complied with, will be captured in the eCRF and the study monitor will prepare a Protocol Deviation/Violation Log.

Corresponding patients may be discontinued from the study at the discretion of the Sponsor/designee. Deviations from the study protocol should not be made other than as part of a protocol amendment. An amendment must be agreed upon by the Sponsor, but not implemented until written IRB/IEC approval is obtained, except where necessary to eliminate an immediate hazard to study patients or when the change(s) involves only logistical or administrative aspects. Protocol deviations/violations and the reason why they occurred will be documented in the Clinical study report (CSR).

5.3.8 Screen Failures and Rescreening

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

Patients may be rescreened once under the following conditions:

- Patients who required treatment for an acute illness that resolved (e.g., a urinary tract infection) or had stabilization of a chronic medical problem (e.g., uncontrolled hypertension).
- Patients who are not on a stable dose of a concomitant medication prior to randomization as per inclusion and exclusion criteria may be re-screened once the stable dose criteria is met.
- Patients with an indeterminate QuantiFERON®-TB Gold test result (for tuberculosis).

The decision to rescreen patients may be optional based on clinical state of the patient and the decision to rescreen will solely be made based on Sponsor’s discretion on a case-by-case basis.

5.3.9 Early Termination of Study or Site

The study may be terminated at any time by the Sponsor for safety concerns due to serious AEs, inability to achieve the recruitment target within reasonable time or if in the Sponsor's judgement, there are no further benefits to be expected from the study. In such a case, the Sponsor or delegate will inform the study Investigators, institutions, and all Regulatory Authorities.

The study can also be terminated by the Regulatory Authority for any reason or at a site level as decided by the Independent Data Monitoring Committee (IDMC), Independent Ethics

Committee or Institutional Review Board (IEC/IRB). The Sponsor may close individual study sites prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of patients.

6.0 STUDY PROCEDURES

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the assessment. In such cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. 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 study team should be informed of these incidents in a timely manner.

Patients should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule. Visits 2, 4, 6 (in the Treatment period) and Visit 8 (in the Follow-Up period) are optional. There is a permissible window of ±1 day both for study visits in the Treatment period (Visit 1 to Visit 7) and during the FU period (after Visit 7 to Visit 16). Every effort should be made to schedule every visit on the exact Day (which is relative to the Baseline visit) as described in the Schedule of Assessments (Table 1).

The assessments to be performed at each study visit will be conducted respecting the order of assessments as follows:

At all visits, the efficacy assessments should be performed first, prior to any other study specific procedure with the only exception of obtaining informed consent at Screening.

6.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the ICF) will be considered enrolled in the study. A Screening number will be obtained by the site using IxRS. In addition, patients will be invited to give informed consent (on a separate ICF) for the pharmacogenetic sampling. The pharmacogenetic assessment is optional and patients will not be excluded from the study if they do not consent to the sampling for this assessment.

6.2 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 Section 5.3.1 and 5.3.2 respectively. Screening procedures must be performed within 15 days prior to randomization.

In addition to obtaining written informed consent, the following assessments will be performed at Screening:

- Assign patient Screening number via IxRS.
- Eligibility evaluation (review of inclusion and exclusion criteria).
- Relevant medical and surgical history, relevant prior medications including all previous treatment/therapies for MG including patient's response and all concomitant medications.
- Complete physical examination including height and weight.
- Vital signs.
- Demographic data (date of birth, gender, race, and ethnicity).
- Efficacy assessments in the order of MGQoL15r, MG-ADL, QMG, and MGC before any other assessments (except for obtaining informed consent).
- Clinical laboratory tests (hematology including hemoglobin, platelet count, white blood cell count with differential count; blood chemistry, including creatinine, creatinine clearance, blood urea nitrogen [BUN], glucose, alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, gammaglutamyl transferase [GGT], C-reactive protein [CRP], alkaline phosphatase, lactate dehydrogenase, uric acid, albumin, potassium, sodium, calcium, thyroglobulin, International normalized ratio or activated partial thromboplastin time (aPTT), and CD19 counts.
- ECG.
- Urinalysis.
- Serum Pregnancy test.
- Viral and bacterial tests (including surface antigen of hepatitis B virus [HbsAg] and anti-hepatitis C antibodies, HIV, and tuberculosis serology).
- Suicidality assessment.
- Assess AEs if any.

6.3 Randomization

The results of all Screening procedures must be available prior to randomization at Visit 1 to determine eligibility for randomization into the study. If a patient meets all the study

eligibility criteria, the Investigator will randomize the patient at Visit 1 via IxRS; if the patient is not eligible, then the patient should be recorded as a screen failure in the IxRS.

On completion of Screening and randomization, study patients will be instructed not to participate in any other clinical study that involves an intervention or collection of data until the completion of the current study.

6.4 Treatment Period

On all dosing days (Visits 1, 3, 5 and 7), the following order of assessments should be respected:

- Complete all pre-dose assessments, including confirmation of eligibility at Visit 1, prior to dosing (efficacy assessments, all blood sampling except for PK sample to be taken post-dose, urine sampling, vital signs, physical examination, ECG) **starting with the efficacy assessments** in the following order:
    - MGQoL15r,
    - MG-ADL,
    - QMG,
    - MGC.
- Randomization of patient in IxRS (at Visit 1).
- Administration of ARGX-113 or placebo.
- Blood sampling for PK post-dose.
- Patients to remain at the site for over a period of 2 hours following infusion.
- Record concomitant medications, suicidality assessment, and assess AEs if any.

The Treatment period will include assessments starting at Visit 1 to Visit 7 (EoT).

6.4.1 Visits 1, 3, 5, and 7

Prior to administration of the IMP (as an IV infusion) at Visits 1, 3, 5, and 7 the following assessments will be performed:

- After review of eligibility criteria, patient will be randomized at Visit 1.

- Efficacy assessments in the order of MGQoL15r, MG-ADL, QMG, and MGC before any other assessments. At least MG-ADL should be done prior to randomization at Visit 1.
- Abbreviated physical examination including (evaluation of body weight) at Visits 1, 3, and 5. Complete physical examination at Visit 7.
- Vital signs.
- Clinical laboratory tests and urinalysis.
- Urine pregnancy test.
- ECG at Visit 1 and Visit 7.
- Anti-drug antibodies at Visits 1, 5, and 7.
- Blood sampling for assessment of PD markers (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies).
- Blood sampling (with an allowed window of 30 minutes prior to start of infusion) for PK assessments.
- Collect blood sample for pharmacogenetic testing (to assess FcRn polymorphisms) in case the patient agrees to participate in optional pharmacogenetic testing and signs separate informed consent at Visit 1. If the blood sample at Baseline is missed, the sample should be drawn at Visit 3 (prior to administration of IMP).
- The IMP (ARGX-113 or placebo) will be administered as an IV infusion over a period of 2 hours at Visits 1, 3, 5, and 7.
- Blood sampling post-dose (with an allowed window of 30 minutes after end of infusion) for PK assessments.
- Review of concomitant medications.
- Suicidality assessment.
- Assess AEs if any.

6.4.2 Visits 2, 4, and 6 (Optional)

- Blood sampling for PK and PD (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies).

- Review of concomitant medications.
- Assess AEs if any.

6.5 Follow-Up Period

The FU period will include assessments starting at Visit 8 to Visit 16 (EoS).

6.5.1 Visit 8 (Optional)

- Blood sampling for PK and PD (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies).
- Review of concomitant medications.
- Assess AEs if any.

6.5.2 Visits 9, 10, 11, 12, 14, and 16

- Efficacy assessments in the order of MGQoL15r, MG-ADL, QMG, and MGC prior to any other assessments.
- Abbreviated physical examination (including weight) at Visits 9, 10, 11, 12, 14. A complete physical examination (including weight) to be conducted at Visit 16.
- Vital signs.
- Clinical laboratory tests, urinalysis.
- ECG at Visit 16.
- Anti-drug antibodies.
- Blood sampling for PK (not on Visits 14 and 16) and PD (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies) assessments.
- Perform urine pregnancy test at Visits 11 and 16.
- The EoS visit will be at Visit 16.
- Suicidality assessment.
- Review of concomitant medications.
- Assess AEs if any.

6.5.3 Visits 13 and 15

- Clinical laboratory tests.
- Blood sampling for PD assessments (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies).
- Suicidality assessment.
- Review of concomitant medications.
- Assess AEs if any.

6.6 Early Discontinuation Visit

In case of early discontinuation visit, the same assessments as scheduled for (Visit 16 or EoS) must be performed where possible as follows:

- Efficacy assessments in the order of MGQoL15r, MG-ADL, QMG, and MGC prior to any other assessments.
- Complete physical examination (including weight).
- Vital signs.
- Clinical laboratory tests, urinalysis.
- ECG.
- Anti-drug antibodies.
- Blood sampling for PD (total IgG, IgG subtypes [IgG 1, IgG 2, IgG 3, and IgG 4], and anti-AChR antibodies) assessments.
- Perform urine pregnancy test.
- Suicidality assessment.
- Review of concomitant medications.
- Assess AEs if any.

6.7 Unscheduled Visit

It is at the Investigator's discretion to initiate an unscheduled visit, if deemed necessary for the patient's safety and well-being (e.g., for a safety FU after completion or discontinuation

to monitor any unresolved AE). All such visits will be documented along with any additional required documentation based on the nature of unscheduled visit.

7.0 STUDY TREATMENTS

7.1 Treatments Administered

ARGX-113 or matching placebo will be administered intravenously as 4 infusions administered one week apart (total volume of 250 mL) at Visits 1, 3, 5, and 7 over a period of 2 hours.

7.2 Identity of Investigational Medicinal Products

ARGX-113 the IMP and related 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 [redacted] who will also provide the Investigator with certificate of analysis, certificate of conformity and European Union Qualified Person (EU QP) release documents.

ARGX-113, the IMP will be provided as a sterile, colorless, clear concentrate solution for intravenous administration in a formulation of [redacted]. The extractable volume from one vial is [redacted] mL. Appropriate dilutions in a [redacted]% Saline solution will be made on site prior to administration.

The placebo will be provided as a sterile colorless, clear concentrate solution for intravenous administration ([redacted] mL in 20R vial) with the same formulation as the ARGX-113 solution but without the active ingredient that is present in ARGX-113. The extractable volume from one vial is [redacted] mL.

All IMPs 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) and Table 3 provides an outline of the IMP and the dosage form and strength for Study ARGX-113-1602.

Table 3 Investigational Medicinal Products

Investigational Medicinal Product	Dosage form and strength	Manufacturer
ARGX-113	20 mg/mL sterile, colorless, and clear concentrate solution for intravenous administration	[redacted]
Placebo	Matching placebo sterile, colorless, and clear concentrate solution for intravenous administration	

7.3 Packaging and Labelling

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

7.4 Storage of Investigational Medicinal Product

The Investigator (or his/her designee) is responsible for the 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 35-47°F) in their secondary packaging, should not be exposed to freezing temperatures, and should be protected from direct sunlight during storage at the clinical site.

Daily minimum/maximum temperature logging at the IMP storage location at the investigational site should be performed.

Further information on how to handle temperature excursion can be found in the IMP management manual (pharmacy manual).

7.5 Method of Assigning Patients to Treatment Group

Once the patient has provided informed consent, the site will enroll the patient and a Screening number will be allocated via IxRS. Upon confirmation of eligibility at Visit 1, the site will randomize the patient via IxRS, which will generate a patient Randomization number.

The randomization code will be held by Cenduit. Patients will be randomized in a 1:1 ratio to ARGX-113 or placebo. No study team members from the Sponsor or the Sponsor's

designated CRO (Quintiles) will have access to this randomization code until after final database lock.

7.6 Selection of Doses in the Study

Based on the preliminary safety and PK/PD data of the aforementioned Phase I study in healthy subjects (ARGX-113-1501), a weekly dose of 10 mg/kg ARGX-113 was selected for investigation in this exploratory Phase II study as this dose regimen resulted in a maximum PD effect and was considered safe.

There was a dose-dependent decrease of serum IgG concentrations following a single dose administration of ARGX-113. There was a maximum decrease of serum IgG concentrations at a dose of approximately 10 mg/kg while a lower dose of 2 mg/kg resulted in less reduction of IgG concentrations. Pharmacodynamic data after multiple dosing showed that a dose of 10 mg/kg either administered every 4 or 7 days resulted in what was anticipated to be a maximum effect on serum IgG concentrations in terms of both depth of the PD effect and time to reach nadir.

As a lower drug exposure and a less frequent dose administrations are considered more convenient for patients, the dose regimen of 4 weekly doses of 10 mg/kg was selected for investigation in Phase II studies. ARGX-113 was found to be safe and well tolerated following administration of four weekly 2-hour IV 10 mg/kg infusions to healthy subjects.

It has been reported that reduction of serum IgG concentrations in MG patients following short-term treatment with plasma exchange, immunoadsorption or IVIg results in a clinically meaningful effect (i.e., amelioration of signs and symptoms)[13, 14].

The impact of reducing serum IgG concentrations with ARGX-113 on the clinical effect of MG patients is currently unknown. Thus, the dose which was found to be safe and resulted in a maximum PD effect was selected for investigation in this study. Additional doses and dose regimens may be considered for future studies.

During this study, no changes in the IP dose will be allowed.

7.7 Timing of Dose for Each Patient

ARGX-113 and placebo will be administered intravenously as 4 infusions administered one week apart over a period of 2 hours at Visits 1, 3, 5, and 7. Patients will be asked to remain at the site for a minimum of 2 hours after the end of infusion as part of routine safety monitoring at Visits 1, 3, 5, and 7.

7.8 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. The IMP and placebo will be identical in physical appearance. The treatment each patient receives will not be disclosed to the Investigator, investigational site staff, patient, Sponsor, the Sponsor's designated CRO (Quintiles) The study will only be unblinded following the database hard lock.

7.8.1 Emergency Unblinding

The process for breaking the blind will be handled through the IxRS. Investigators are strongly discouraged from requesting the blind to be broken for an individual patient, unless there is a patient safety issue that requires unblinding and would change patient management. If possible, Investigators/Sponsor's medical expert should discuss with the Medical Monitor at Sponsor's designated CRO (Quintiles) before approaching IxRS to break the blind. If the blind is broken, it may be broken for only the patient in question.

The Sponsor and Sponsor's designated CRO (Quintiles) Medical Monitor must be notified immediately if a patient and/or Investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and electronic case report forms (eCRFs). Once unblinded, the patient will be discontinued early from the study.

7.9 Prior and Concomitant Treatments

All concomitant medications whether allowed or not must be recorded in the eCRFs. All clinically relevant prior medications received by the patient including previous treatment for MG with patient's response at least 12 months before Screening must be recorded in the eCRFs.

7.9.1 Prohibited Medications during the Study

The following medications will not be permitted during the study and will result in early discontinuation from the study when they need to be started:

- Any IgG therapy;
- Introduction of a new immunosuppressant that the patient was not already taking at Screening;
- Dose increase in the immunosuppressant that the patient was taking from Screening;

- Rituximab, belimumab, eculizumab, or any monoclonal antibody for immunomodulation;
- Vaccines;
- Therapeutic PE.

7.9.2 Rescue Therapy

Patients are eligible for rescue therapy as judged by the Investigator on the basis of parameters such as changes in MGQoL15r, MG-ADL, QMG, and MGC on any study day. Rescue therapy will be determined by the Investigator based on an overall clinical assessment and could include IVIg, PE, increase in the dose and frequency of SoC or any other treatment chosen by the Investigator. In this study, ARGX-113 may interfere with the efficacy or duration of efficacy of IVIg considering the half-life of IVIg. Additional details about ARGX-113 is present in Section 2.2.

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 contract research organization (CRO, Quintiles); where possible prior to actual implementation of the rescue therapy.

If rescue therapy is administered, patients need to be discontinued from the study. For patients who discontinue the study early, all the procedures listed for the Early Discontinuation (ED) visit (same procedures as for the End-of-Study [EoS] visit or Visit 16) in the Schedule of Assessments (Table 1) are to be performed (early discontinuation visit) prior to starting on rescue therapy wherever possible.

7.10 Medical Care of Patients after End-of-Study

After a patient has completed the study or has withdrawn/discontinued early, usual treatment will be administered, if required, in accordance with the study site's SoC and generally accepted medical practice depending on the patient's individual needs. The Sponsor will not provide any additional care to patients after they withdraw/discontinue early or complete the study neither will the IMP be provided on a compassionate use program.

7.11 Treatment Compliance

The Investigator should promote compliance by stating that compliance is necessary for the patient's safety and the validity of the study. 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.

7.12 Handling Missed Doses of the Investigational Medicinal Product

If the patient misses more than one dose of the IMP he/she may be replaced although may continue in the study and maybe evaluable for safety and efficacy evaluation, for details refer to Table 2.

7.13 Accountability of Investigational Medicinal Product

The Investigator or delegated site staff is responsible for ensuring that the IMP received at the clinical site is inventoried and accounted for throughout the study.

Infusion of the IMP must be completed under the supervision of the Investigator, by a qualified member of the clinical staff. The Investigator or delegated site staff must maintain accurate records, demonstrating date and amount of IMP supplied and by whom.

The Sponsor's designated site monitor will periodically check the supplies of IMP held by the Investigator or pharmacist to ensure accountability and appropriate storage conditions of all IMP used.

Unused IMP must be accessible for verification by the site monitor during on-site monitoring visits. Used IMP should be kept on site and its accountability will be checked by the site monitor. Only after appropriate verification and confirmation from the site monitor, used IMP (vials) can be discarded/destroyed in accordance with the site procedures.

After the database lock, any remaining unused IMP will be returned to the Sponsor, or destroyed at the clinical site with the Sponsor's written permission (in this case a certificate of destruction will be provided and filed in the Trial Master File).

Hazardous materials such as used needles, syringes, and infusion bags, containing hazardous liquids, should be discarded immediately after use in a safe manner and must not be retained for drug accountability purposes or verification by the site monitor.

7.14 Storage of Blood Samples in the Study

The leftover of samples that are left after the analysis per protocol is complete and other remaining samples (of all samples except for samples taken for clinical laboratory tests) will be stored for up to 15 years for future additional research. Patients will be asked to confirm if

they allow additional storage of samples in the study ICF to address any scientific questions related to ARGX-113 or MG.

8.0 SAFETY, EFFICACY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

8.1 Safety

Safety assessments will consist of monitoring and recording all AEs, including SAEs, and 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 study in all patients who receive at least 1 dose of the IMP. As discussed in Section 8.1.1.4, any pregnancy that occurs while a patient is enrolled in the study will also be monitored and reported according to the appropriate regulations.

8.1.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study 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 study 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).

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 associated with clinical signs and symptoms that are considered clinically significant, 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.

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the disease under study and/or increase in the symptoms of the disease and should be considered as disease progression and not an AE.

Adverse Drug Reaction (ADR): Any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject.

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 were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before a study are not considered SAEs or if the illness or disease which caused hospitalization existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. However, the condition for which the surgery is required may be an AE.
- Results in persistent or significant disability or incapacity;
- 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 and Unexpected Adverse Reactions

Any suspected adverse reaction that is serious, unexpected, and considered to be related to drug exposure is defined as a suspected unexpected serious adverse reaction (SUSAR).

An unexpected AE is any adverse drug event, which is not listed in the current Investigator's Brochure 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. The following examples provide types of evidence that would suggest a causal relationship between the IMP and the AE:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- An aggregate analysis of specific events observed in a clinical study (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

An untoward and unintended post-dosing response to a non-study 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 study procedures. The action taken with the investigational drug and the outcome of the event must also be recorded.

Overdose

For the purposes of this study, exceeding the dosage requirements specified in this protocol represents an overdose. In case of suspected overdose, the patient should be treated according to standard medical practice based on the Investigator's judgment.

Severity

All AEs observed will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The NCI CTCAE is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. Grade refers to the severity of the AE. If a particular AE's severity is not specifically graded by the guidance document, the Investigator is to use the general NCI-CTCAE definitions of Grade 1 through Grade 5 following his or her best medical judgment. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Relationship

The causal relationship between the IMP/study 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 reasonable 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 CIOMS. Unrelated and Unlikely will be clubbed into "Unrelated" and Related, Possible and Probable will be clubbed into "Related" for final reporting purpose.

8.1.1.1 Reporting of Adverse Events and Serious Adverse Events

All AEs, that occur during the study from signature of informed consent until EoS (Visit 16), 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, stop date (when applicable), severity, action taken, outcome, and relationship to IMP, and to study 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 study personnel: 'Have you had any health problems since the previous visit/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 study after signature of informed consent, whether or not related to the IMP, must be reported immediately (within 24 hours of the study site's knowledge of the event). All SAEs will be recorded (within 24 hours) on the electronic 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 will then be automatically sent by email to the Sponsor's designated CRO (Quintiles) safety mailbox via the electronic data capture (EDC) system. In case the EDC system is not functioning correctly or the system is down, all SAEs should be reported by fax/email to Sponsor's designated CRO (Quintiles) using the SAE paper report form.

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.

All SAEs that are spontaneously reported within 30 days of a patient's last visit are to be collected and reported as previously described.

Additional follow-up information should be completed and entered on an SAE report form in the eCRF with again a copy automatically sent to the Sponsor's designated CRO (Quintiles) by email via the EDC system.

8.1.1.2 Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

The Sponsor's designee will be responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, ethics committees, and Investigators, in

accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The Sponsor's designee will also prepare an expedited report for other safety issues where applicable.

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

8.1.1.3 Follow-Up of Adverse Events and Serious Adverse Events

Any AEs observed from signing the informed consent to the end of the study will be followed up to resolution. 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.

All AEs that occur after the last dose of the IMP should be (pro-actively) followed-up and assessed by the Investigator until (EoS visit or Visit 16) or for 30 days after the early discontinuation visit (regardless of discontinuation occurring in Treatment period or FU period), and until satisfactory resolution or stabilization.

Serious AEs will be captured and followed up until resolution (if needed, also after the EoS visit).

All SAEs that are spontaneously reported within 30 days of a patient's last dose of IMP and/or last visit (EoS visit or Visit 16) are to be collected and reported as previously described (as per Section 8.1.1.1) and will be followed-up regardless of the Investigator's opinion of causality. The Investigator should follow each SAE until the event has resolved to the baseline grade or better, the event is assessed as stable by the Investigator, until the patient is lost to follow-up, or until the patient withdraws consent. If the patient is lost to follow-up, the SAE will be categorized based on the Investigator's last assessment. Every effort should be made to follow all SAEs considered to be related to IMP or study procedures until an outcome can be reported. During the study 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 study should be followed until pregnancy outcome.

For SAEs, nonserious 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.

8.1.1.4 Reporting and Follow-Up Requirements for Pregnancies

8.1.1.4.1 Pregnancies in Female Patients

A serum pregnancy test will be conducted in all females of childbearing potential at Screening, and urine pregnancy tests will be conducted locally thereafter at Visits 1, 3, 5, 7, 11, and 16 as presented in the Schedule of events (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. The patient should be discontinued early from the study treatment as soon as the pregnancy is known and the following should be completed:

- The patient should immediately discontinue from the study.
- The patient should have an early discontinuation visit.
- All assessments for early discontinuation visit (See Section 5.3.4 and 6.6) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the patient withdraws informed consent.

The Investigator must inform the patient of 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.

Full details will be recorded on a Pregnancy Report eCRF and submitted via the Electronic Data Capture (EDC) system, and reporting details will be detailed in the study manual. The Investigator will update the Pregnancy Report eCRF 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 eCRF page.

8.1.1.4.2 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 study and up to 90 days after the patient received the last infusion. A Pregnancy Report eCRF should be completed by the Investigator within 1 working day after learning of the pregnancy and submitted via the EDC system. 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 eCRF 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 co-operation with the treating physician and/or obstetrician.

8.1.2 Clinical Laboratory Evaluations

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be collected and analyzed at a central lab as indicated in the Schedule of Assessments (Table 1). Patients need to be fasting for at least 8 hours prior to the sampling for clinical lab tests.

Urine pregnancy test and ECG will be done at local lab.

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

A serum pregnancy test will be performed (on the samples taken for clinical laboratory tests) for all patients of childbearing potential at Screening, and a urine pregnancy test will be performed locally at the site (can be done on the urine sample taken for urinalysis) at Visits 1, 3, 5, 7, 11, and 16.

The total volume of blood will not exceed 226 mL for the duration of the study.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. 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.

8.1.3 Vital Signs, Physical Examination, and ECGs

Assessment of vital signs (supine blood pressure, pulse rate, and oral body temperature) will be performed at the time points indicated in the Schedule of Assessments (Table 1).

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

A complete physical examination will be performed at Screening, Visit 7, and at Visit 16/EoS/ED visit as indicated in the Schedule of Assessments (Table 1) and will include an assessment of general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal/extremities, abdomen, breast, and cardiovascular, respiratory, neurological, and genital/rectal systems. An abbreviated examination will be done at all other visits. In addition, weight will be assessed at each of these time points.

On IMP infusion days, physical examination, including weight, will be assessed pre-dose.

Height will be measured at Screening visit only. For assessment of height and weight, patients will be required to remove their shoes and wear light indoor clothing for these measurements.

The digital ECG assessments will be performed at the time points indicated in the Schedule of Assessments (Table 1).

A ECG will be recorded in the supine position after the patient has rested in this position for at least 10 minutes. The assessment on heart rate, PR, QT, and QRS intervals will be locally read by the Investigator or delegate.

8.1.4 Suicidality assessment

As is recommended for studies involving a biological product for a neurological indication, a prospective assessment for suicidal ideation and behavior will be included in this clinical study.

This so called suicidality assessment will be conducted by specifically asking the following question, derived from the Patient Health Questionnaire item 9 (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 scheduled visit, except the optional visits to collect PK/PD blood samples, 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.[2]

8.1.5 Medical History

All significant findings that are present at Screening must be reported on the relevant medical history/current medical conditions page of the eCRF.

As part of medical history details must include and is not limited to all previous treatment/therapy taken for MG, patient's response to each of the previous MG treatment/therapy received.

8.1.6 Independent Data Monitoring Committee

An IDMC consisting of members who are independent from the Sponsor will be established. The IDMC will be established prior to the enrollment of the first patient in the Treatment period. The IDMC membership will have 4 independent members (3 physicians and 1 unblinded biostatistician), including at least one neurologist with expertise in treatment of MG, as appropriate. The IDMC quorum will comprise of 3 independent members with 2 physicians and 1 unblinded biostatistician. Three data review meetings are planned. The IDMC will review the safety data during the first and second data review meeting, and during the third data review meeting, efficacy and safety data will be reviewed.

The IDMC is responsible for reviewing and evaluating unblinded safety data collected after 8 patients complete treatment period and have had a minimum of 2 weeks follow-up. The IDMC will subsequently review unblinded safety data after 16 patients complete treatment period and have had a minimum of 2 weeks follow-up and after the final database lock all safety and efficacy data will be reviewed for all randomized patients.

The IDMC may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The IDMC will review the unblinded safety data during the Data review meetings. The roles and responsibilities of the IDMC, their operational procedures, and method of communication with argenx will be described in a separate IDMC charter.

Members of IDMC will not be Investigators in the study nor will they have any conflict of interest with the Sponsor.

8.2 Efficacy

8.2.1 Appropriateness of Measurements

Efficacy assessments will be done using MG-ADL, as QMG, MGC, and quality of life will be measured using MGQoL15r. These assessments will be completed at Screening, and have to be performed pre-dose on all IMP infusion days i.e., at Visits 1, 3, 5, 7; in addition to Visits 9, 10, 11, 12, 14, and 16.

8.2.2 Myasthenia Gravis-Activities of Daily Living

The MG-ADL is an 8-item patient-reported scale 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 scores indicating more impairment. The assessments to be performed using MG-ADL does not require any equipment or training. The assessments that will be performed using MG-ADL is included in Appendix 14.1.

8.2.3 Quantitative Myasthenia Gravis

The QMG quantifies disease severity based on impairments of body functions and structures as defined by the International Classification of Disability and Health.[15]

The QMG consists of 13 items 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 scores indicate more severe impairments. It is based on quantitative testing of sentinel 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 physician's examination. The items that will be tested is included in Appendix 14.2.

8.2.4 Myasthenia Gravis Composite

The MGC has 10 items combining physician 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 possible score is 50, with higher scores reflecting more severe impairments. The items that will be tested is included in Appendix 14.3.

8.2.5 15-Item Quality of Life Scale for Myasthenia Gravis

The 15-item Quality of Life scale for Myasthenia Gravis (MGQoL15r) 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 MGQoL15r 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 score of 30. The questions that patients should provide a response to assess their quality of life is included in Appendix 14.4.

8.3 Pharmacokinetics

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

Pharmacokinetic calculations will be performed by Quintiles using Quintiles SOPs and standard non-compartmental and/or compartmental methods, as appropriate.

The appropriate PK parameters will be calculated after single (Visit 1) and multiple administrations (Visits 3, 5, and 7) of ARGX-113 using individual concentration data in plasma and actual sampling times:

C_{max}	maximum observed plasma concentration
t_{max}	the time of occurrence of C_{max}
C_{trough}	plasma concentration observed at pre-dose at Visits 3, 5, and 7
$t_{1/2,\lambda z}$	the apparent terminal half-life, calculated from $(\ln 2)/\lambda_z$ (Visit 7 only)
R_{ac}	accumulation ratio, calculated as Visit 7 C_{max} /Visit 1 C_{max}

8.4 Pharmacodynamics

The PD markers (anti-AChR antibodies and immunoglobulin-G and its sub-types) will be measured on at the times indicated in Table 1. Results will be determined using a validated assay. The actual date and time of collection of blood sample will be recorded in the relevant section of the eCRF.

8.5 Additional Assessment of Immunoglobulins

The blood sample used to assess the PD markers, will be used to assess IgA, IgM, IgE, and IgD.

8.6 Anti-drug Antibodies

Blood sample to assess ADA will be collected pre-dose at Visits 1, 5, and 7. Subsequently ADA will be assessed at Visits 9, 10, 11, 12, 14, and 16 during the Follow-up period.

8.7 Pharmacogenetics

This study includes an optional Pharmacogenetic assessment which requires signature of a separate informed consent if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. As this is an optional assessment, if the patient refuses consent he/she will not be excluded from the study. In this study, pharmacogenetic analysis will not be used for making regulatory judgments pertaining to the safety or efficacy of the IMP.

However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of new genomic biomarkers.

If patients consent for this optional assessment, a blood sample will be collected prior to first dosing on (Visit 1) and will be stored for pharmacogenetic analysis (limited to the assessment of FcRn polymorphisms). In case the blood draw at Baseline is missed, the sample should be taken at Visit 3 prior to the administration of IMP.

Blood samples taken for this pharmacogenetic analysis will be stored for up to 15 years at Quintiles Q2 lab during which the assessment of FcRn polymorphisms may be done on the DNA derived from the samples, and these will not be used for additional gene analysis.

9.0 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 as described in the Clinical Study Agreement. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study 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 study documents, refers to the Investigator or authorized study personnel that the Investigator has designated to perform certain duties. Sub-Investigators or other authorized study 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.
- Early site visits post-enrollment.
- Routine site monitoring.
- Ongoing site communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the CSR.

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

9.3 Monitoring

The Sponsor has engaged the services of a CRO, named Quintiles, to perform all monitoring functions within this clinical study. Sponsor's designated CRO (Quintiles') monitors will work in accordance with Quintiles' standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly prior to any study related procedures performed and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also control adherence to the protocol at the study site. They will arrange for the supply of IMP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. The Investigator must permit study related monitoring by providing direct access to source data and to the patients' medical histories. The Clinical Monitors will perform monitoring visits at each site at regular intervals during the study and after the study has completed, as appropriate. The monitor will make written reports to the Sponsor on each occasion when contact with the Investigator is made, regardless of whether it is by phone or in person.

Monitoring visits must be conducted according to the applicable ICH-GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During monitoring visits, entries in the eCRFs will be compared with the original source documents (source data verification). For this study, the data will be 100% checked and verified.

9.4 Data Management and Coding

Data generated within this clinical study will be handled according to the SOPs of the Data Management and Biostatistics departments of the Sponsor's designated CRO (Quintiles).

Data for this study will be recorded via InForm 5.5 EDC system using eCRFs. It will be transcribed by the site from the paper source documents onto the eCRF. The information collected on eCRFs must be identical to the corresponding information appearing in original source documents. There are no exceptions to this rule. Appropriate training and security measures will be completed with the Investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study patients at the site.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit. 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. The Investigator must verify that all data entries in the eCRFs are accurate and correct.

As a matter of regulation, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs. The Investigator should also ensure that patient submits completed and correct questionnaires. Prior to submission, 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 on the eCRF and SAE data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate study site staff will answer queries sent

to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time, and date stamp are captured.

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 study. They 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. Instructions for the completion of eCRFs will be provided.

The eCRFs will be considered complete when all missing, incorrect and/or inconsistent data have been accounted for. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF using appropriate item or form level comments.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study 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 study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

The eCRF records will be automatically appended with the identification of the creator, by means of their unique User Identification (ID). Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledge that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

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.

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 concomitant medications.

9.5 Quality Assurance Audit

Study sites, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or Sponsor's designated CRO (Quintiles) on behalf of Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

10.0 STATISTICS

The statistical analyses will be performed by Sponsor's designated CRO (Quintiles) using statistical analysis system (SAS®), (SAS Institute, Cary, NC, USA) version 9.2 or higher. The SOPs and work instructions of Sponsor's designated CRO (Quintiles') will be used as the default methodology if not otherwise specified.

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

10.1 Determination of Sample Size

Approximately 36 patients will be screened in order to randomize approximately 24 patients (12 patients per treatment arm) to get at least 20 patients who have received at least 3 doses of IMP (either ARGX-113 or placebo) and who completed at least 2 weeks of follow-up period post last dose (See Appendix 14.6). Patients may be replaced in certain circumstances. Possible scenarios in which a patient may be replaced is mentioned in Table 2. Final decision for replacement of patients will be done on a case-by-case basis in consultation with the Medical Monitor at the Sponsor's designated contract research organization (CRO, Quintiles) and/or the Medical Director at the Sponsor's end.

10.2 Analysis Population

The analysis of data will be based on different analysis sets according to the purpose of analysis. The decision regarding validity of data for each of the analysis sets will be based on a blinded review of data, which will occur prior to declaring database-lock and before unblinding of data for analysis.

- **Randomized Population**: Any patients who have been allocated to a randomized treatment arm, regardless of whether they received the planned treatment or not.
- **Full Analysis Set (FAS)**: Patients will be considered under planned treatment for analyses based on FAS. The secondary endpoints analysis will be on the FAS, defined as all randomized patients who had an evaluable efficacy endpoint.

The efficacy endpoint will be considered evaluable when the following condition is met:

- At least one MG-ADL, QMG, MGC, MGQoL15r scores are available within one of the post-baseline assessment up to Visit 16 with the corresponding Baseline value.

- **Safety Population:** The safety population considered for safety analyses will be the randomized population who received at least one dose or part of a dose. The safety population will be analyzed according to the treatment actually received.
- **PK analysis set:** PK analysis population considered for PK analysis will be the randomized population who have at least one plasma concentration data value available for ARGX 113.

10.3 Patient Disposition, Characteristics and Concomitant Medication

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, enrolled, randomized, completed, as well as the number of dropouts, with reasons for discontinuation and major protocol deviations or violations.

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

A list of protocol violations will be identified and discussed with the Investigator to categorize as major or minor and the same will be reported.

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 observation [n], mean, standard deviation (SD), median, minimum and maximum) and for categorical measures (sample size, frequency, and percent). Treatments will be compared by using t-tests for quantitative measures and the Fisher's exact test or the Chi-squared test for categorical measures. Patient characteristics include but are not limited to age, gender, race, weight, and BMI.

Categorical use of concomitant medication will be summarized by treatment with frequency and percentage. All concomitant medications used will be listed. Exposure to the IMP, i.e., total amount of IMP received, will be summarized and listed for all patients.

10.4 Statistical Methods

Safety, tolerability, efficacy, PK, and PD data will be listed and summarized by treatment group using descriptive statistics. Graphical representations of data will be presented as deemed appropriate. No formal hypothesis testing will be conducted in this study, p-values if presented are to be interpreted descriptively. Continuous variables will be summarized by descriptive statistics ([n], mean, SD, median, minimum, and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Details of statistical analysis methods will be provided in the SAP that will be prepared and signed off prior to unblinding and database lock.

10.4.1 Primary Endpoint Analyses

10.4.1.1 Adverse Events

Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity after the first administration of the IMP.

Summaries over SOC, PT and listings of AEs leading to death, SAEs, AEs, and AEs that led to discontinuation of study treatment will be presented. Summaries will also be presented by relationship to IMP and severity of the AE.

10.4.1.2 Vital Signs Measurements, Physical Findings and Laboratory assessments

Summaries and listings of data for vital signs, hematology, clinical chemistry and urinalysis laboratory tests, ECGs, suicidality assessments, and physical examination findings will be presented. Appropriate data will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and clinical chemistry tests, listings of patient data will also flag up any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and clinical laboratory data will be reported in System International (SI) units.

For ECG variables, the QT correction factor will be based on both the Bazett and Fridericia formulae (QTcB and QTcF). Categorical summaries of absolute QT, QTcB and QTcF values and change from (Baseline) values in QT, QTcB and QTcF values will be presented by treatment and visit.

10.4.2 Secondary Endpoint Analyses

10.4.2.1 Analysis of Scales

Analyses of data derived from scales (MG-ADL, QMG, MGC, and MGQoL15r) will be based on FAS. Actual score, change from Baseline and maximum reduction from Baseline will be summarized descriptively.

Analyses of the change from Baseline in efficacy rating scales will be performed using a mixed- model repeated measures (MMRM) analysis from Visit 1 to Visit 16. The models included the fixed treatment, baseline score and patient as a random effect. Appropriate covariance structure will be used. At each visit day, IMP will be compared with placebo and

model-based Least Squares Means for the treatment effects, 95% CIs and p-values will be calculated for within and between treatment comparisons.

Figure for change from Baseline in total score (last observation carried forward) in patients will be presented. Number and percentage of patients by levels of point reduction will be presented by horizontal bars for IMP and placebo.

10.4.2.2 Analysis of Pharmacokinetic Parameters

Pharmacokinetic analyses will be performed based on the PK population. Plasma concentrations at each sampling time point will be summarized for ARGX-113 by the following summary statistics:

- Arithmetic mean calculated using untransformed data
- SD calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations
- Number of observations ≥lower limit of quantification (LLOQ)

Geometric mean plasma concentrations against protocol time will be shown by patient in both linear and log scales, respectively. Note that the values of geometric mean (G_{mean}) ± SD will also be shown in this graph using vertical lines.

The following summary statistics will be presented for all the PK parameters except for t_{max}

- G_{mean}
- GCV
- Arithmetic mean calculated using untransformed data
- SD calculated using untransformed data
- Minimum
- Median
- Maximum
- Number of observations

The following summary statistics will be presented for the PK parameters t_{max}

- Number of observations
- Median
- Minimum

- Maximum

10.4.2.3 Analysis of Pharmacodynamic Parameters

Continuous PD parameters summarized with descriptive statistics including geometric mean. Pharmacodynamic parameters include total IgG, IgG subtypes, anti AChR antibodies. Further details will be described in the SAP.

10.4.2.4 Anti-Drug Antibodies (ADA) Analyses

Frequency and percentage of ADA response will be presented and listed. ADA response data will also be summarized as proportions along with their 95% CIs using exact test separately for each treatment. Further detail analyses will be presented in the SAP.

10.5 Interim Analyses

Not applicable.

11.0 ETHICS

11.1 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 study may begin at the study 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 study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

11.2 Ethical Conduct of the Study

This study 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 study will be conducted.

11.3 Patient Information and Informed Consent

The informed consent form (ICF) will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is enrolled into the study. A separate ICF will be given in case a patient consents for Pharmacogenetic analysis and for Pregnancy in case 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 study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative, after the receipt of detailed information on the study.

All ICFs must be available in the local and vernacular languages required at the site and include patient information sheets/brochures that outline the study 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 an impartial witness who is literate and not affiliated with the study. The patient having understood the information given to him/her in the presence of an impartial witness will thumbprint the ICF(s) and the same will be countersigned by the impartial witness. 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 consent form.

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 legal 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 consent form.

11.4 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.

Sponsor or representative will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a Sponsor or representative physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files.

12.0 STUDY ADMINISTRATION

12.1 Administrative Structure

Table 4 Administrative Structure

Clinical Trial Supply Management B & C Group Watson & Crick Hill Rue Granbonpré 11 B-1435 Mont-Saint-Guibert Belgium	**Clinical Laboratory** Q2 Lab Solutions The Alba Campus, Rosebank Livingston, West Lothian EH54 7EG, United Kingdom **And** Q2 Lab Solutions 27027 Tourney Road Valencia, CA 91355 USA **Analysis of PK-PD, Anti-drug antibodies** SGS Cephac Europe SAS 90 Avenue des Hauts de la Chaume BP. 28 86281 Saint-Benoit Cedex France
Study Monitoring Quintiles Parque Empresarial Cristalia Vía de los Poblados, 3 Edificio 7/8, 5 Planta 28033 Madrid - Spain	**Drug Safety Reporting** Quintiles Ireland Limited Estuary House, East point Business Park, Alfie Byrne Road, Dublin 3 - Ireland
Data Management Quintiles, India 3rd Floor, Etamin Block, Prestige Technology Park II, Sarjapur-Marathahalli Outer Ring Road Bengaluru-560103, Karnataka - India	**Biostatistics** Quintiles Research (India) Pvt Ltd 12 Floor , G.Corp Tech Park Thane-Ghodbunder Road Kasarvadavali , Thane (West)-400615, Maharashtra - India
Medical Monitoring Quintiles, 500 Brook Drive, Green Park Reading, Berkshire, RG2 6 UU, UK Telephone number +[redacted]	**Study Report Preparation** Quintiles, India Quintiles, I Floor, 'A' wing Salarpuria Supreme #92/5, Outer Ring Road, Munnekolala Village, Marathalli Bengaluru -560037, Karnataka - India

12.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (including regulatory documents, eCRFs, signed patient ICFs, source documents, relevant correspondence, AE reports, and all other supporting documentation) as required by the applicable national regulatory requirements. The study site should plan on retaining such documents for approximately 15 years after study completion. The study site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IMP.

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

The United States (U.S) Food and Drug Administration (FDA) regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after the last marketing application approval in an ICH region or after at least 15 years have elapsed since formal discontinuation of clinical development of the IMP will notify the PI of these events.

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

For studies conducted outside the U.S. under a U.S. Investigational New Drug (IND), the Principal Investigator must comply with U.S. FDA IND regulations and with those of the relevant national and local health authorities.

12.3 Direct Access to Source Data/Documents

The Sponsor or designee and auditor may access patient records for the purpose of monitoring this study, auditing, and managing progress details. The Investigator must be fully aware that the Sponsor or designee and auditor can inspect, verify, or copy documents to verify patient chart and eCRF records. Such information must be kept confidential and must have locked facilities that allow for this. Patient identification number and not the patient's name will be recorded on all documents related to the study. The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient randomized into the study.

12.4 Investigator Information

12.4.1 Investigator Obligations

The Investigator is responsible for ensuring that all study site personnel, including Sub-Investigators, adhere to all applicable regulations and guidelines, including local laws

and regulations, regarding the study, both during and after study completion. The Investigator is responsible for informing the IRB/IEC of the progress of the study and for obtaining annual IRB/IEC renewal. The Investigator is responsible for informing the IRB/IEC of completion of the study and will provide the IRB/IEC with a summary of the results of the study.

12.4.2 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 study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for GCP and applicable regulatory requirements. The study will not be able to start at any site where the Investigator has not signed the protocol.

12.4.3 Publication Policy

All information regarding ARGX-113 supplied by the Sponsor to the Investigator and all data generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The results of the study will be reported in a CSR.

The CSR 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 study 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. Study subject 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 studies as required by law.

12.5 Financing and Insurance

Sponsor will fund the study as outlined in the Clinical Trial Agreement. All direct costs associated with the conduct of the study and laboratory investigations will be paid for by the Sponsor.

Sponsor will obtain adequate global/local insurance for the study participants including the study patients for the required duration of time.

Sponsor will provide insurance coverage with respect to any liability caused by the IMP and/or study-related procedures in connection with this clinical study. Liability and insurance provisions for this study are specified in the Investigator's contract. The terms and conditions will apply as specified in the policy document.

13.0 REFERENCES

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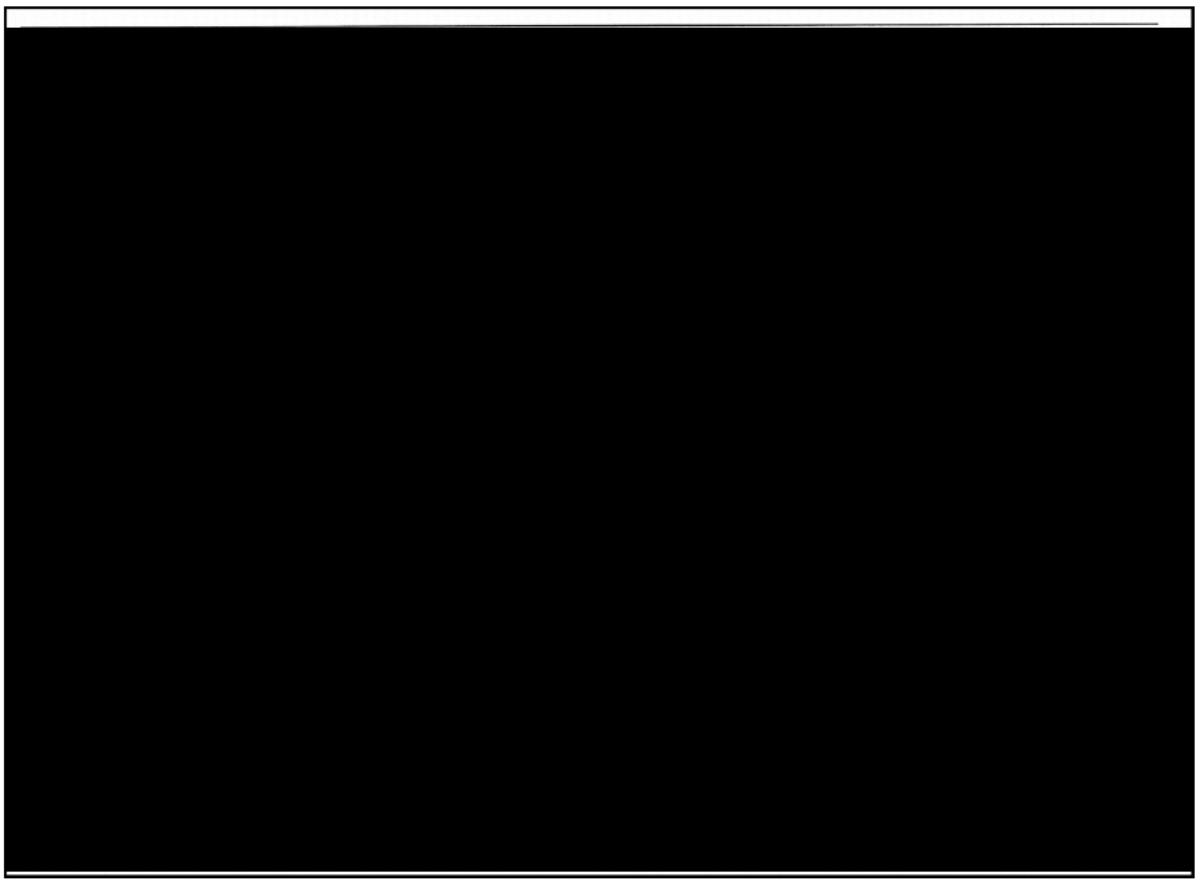
14.0 APPENDICES

14.1 Appendix 1: Myasthenia Gravis-Activities of Daily Living



14.2 Appendix 2: Quantitative Myasthenia Gravis score

QUANTITATIVE MYASTHENIA GRAVIS TESTING FORM

Patient Name:_____Patient #:_____Date:
MR#:_____DOB:__ Sex:___ Ht.(in)_____Wt.(kg):_____
Evaluator:_____Handedness:_____Leggedness:_____Time of Exam:_____
Anticholinesterase Medication:_____
Comments:_____

[redacted]

TOTAL QMG SCORE: _____

GENERAL INSTRUCTIONS

1. Patients must be off pyridostigmine (or any acetylcholinesterase inhibitor medication) for twelve (12) hours prior to testing, (if medically safe to do so).

2. Perform the tests in the order given in this Manual and shown on the Videotape.

3. Calibrate the respiratory equipment on the day of the test, per manufacturers' instruction, before the test begins. Place the calibration record in folder in an accessible place.

4. For all measurements, record actual numbers as well as grade, i.e., if it takes 30 seconds before a patient sees double, record on the far right box 30/1 for 30 seconds and a grade of 1.

5. Patients must remain seated for the respiratory test.

6. At the end of the scoring sheet, add up the grade for that patient and that becomes the Total QMG Score.

QUANTITATIVE MG SCORE

I. DOUBLE VISION:

Patients' preparation: Patient is sitting. Ask if the patient is experiencing double vision looking straight ahead. If yes, record 0/3 (actual time/grade) on the scoring sheet. If no, ask the patient to look to the right for just an instant and then to the left without moving their head. If the patient sees double in only one direction, record side and record result as 0/3. If there is no eye movement, record as 0/3. If the patient does not see double, or sees double in both directions, have them perform the test as described below gazing to the right.

Explanation to patient: "I need for you to face forward. When I ask, look over to your right (left) side without turning your head. If or when you start to see double, please let me know."

Notes to examiner: Patient's head will usually start to turn in the direction of the gaze. Try to maintain the head in a forward position. Record the time and grade. Example: double vision is evident at 15 sec. In the scoring section, record 15/1.

II. PTOSIS (upward gaze):
Patients' preparation: Patient is sitting. Ask the patient to look straight ahead. If the upper lid is touching the pupil, record as 0/3. Ask the patient to look up at the ceiling without moving the head.

Explanation to patient: "I need you to face forward. When I ask, look up at the ceiling without moving your head. Keep looking up until I tell you to relax."

Notes to examiner: Patient's head will usually start to move up. Try to maintain the head in a forward position. Record time and grade when you see either eyelid (lashes) start to droop. Ex: Right eyelid starts to droop at 9 sec., record 9/2. If neither eyelid touches the pupil, record 60/0.

III. FACIAL MUSCLES:

Patients' preparation: Patient is sitting facing forward.

Explanation to patient: "Squeeze your eyes shut. Do not allow me to open your eyes."

Notes to examiner: If the patient cannot fully close either eye shut, record the grade as 3. No time score is needed on this test. Record grade of the weaker eye.

IV. SWALLOWING:

Patient's preparation: Patient is sitting. Four ounces of water (no ice) is poured into a cup. The water should be no cooler than water fountain cool.

Explanation to patient: "I need for you to drink this water as you normally would."

Notes to examiner: Listen for coughing and/or throat clearing during the test and immediately post test.
Don't ask patients to drink faster than what they feel comfortable doing.

V. SPEECH:

Patient's preparation: Patient is sitting.

Explanation to patient: "Count out loud from 1 to 50 at a comfortable pace."

Notes to examiner: This is one of the most difficult tests to score because of varying accents. Record number when you notice a nasal or slurring of the speech.

VI. RIGHT & LEFT ARM OUTSTRETCHED:

Patient's preparation: The patient needs to be sitting in a chair with both feet on the floor. They must be seated without leaning against the back of a chair. Test both arms at the same time. Arms need to be out to the side at 90^{o}, palms down. (Demonstrate this position). If the patient cannot raise an arm out to
90^{o} due to a shoulder problem, do not test that arm. The elbows are extended through full mechanical range.

Explanation to patient: "I need for you to hold both arms out to the side like this. Keep the arms out as long as possible. If one arm tires more than the other, you may lower that arm and keep the other arm up."

Notes to examiner: It is not uncommon that the arms start to droop. If the arms drop more than 10^{o} from starting position, remind the patient to pull the arms up. If the patient can pull the arms up but cannot maintain that position for longer than two seconds, stop the test. If one arm is lowered, be careful that the patient does not start to lean to the side that the arm was lowered to give the appearance that he/she is maintaining a 90^{o} angle. Record time/grade (ex: 45 sec for right arm is 45/2; whereas 100 sec for left arm is 100/1).

VII: FORCED VITAL CAPACITY:

Patient preparation: Patients must remain seated for this test.

Explanation to patient: "I am testing total lung capacity. I am going to ask you to hold this mouthpiece away from your face. I will then place the nose-clips on your nose. I will tell you to take a deep breath in, and then place the mouthpiece in your mouth. You will blow out as hard and as fast as you can. Keep blowing until I tell you to stop.

Notes to examiner: We are only testing FVC. A minimum of three trials and a maximum of five trials will be performed. The goal is to get the best two trials within 5% of each other. Give a lot of encouragement. Record best FVC (liters and percentage) and grade on sheet, (ex: 2.55 - 60% / 2).

The "normal" FVC values, and therefore the percent predicted calculations can vary with the spirometer that is used. Some spirometers come with specified normal values. That is why the same spirometer should be used each time you test a subject. For multi-site studies, parameters and normal values should be decided so that all sites are using the same information.

VIII: RIGHT & LEFT HAND GRIP:
Patient preparation: Patient is sitting in a chair. The elbow should be at 90^{o}. Support should be under the medial aspect of the forearm and under the dynamometer.

Explanation to patient: "I am testing grip strength. I need for you to squeeze as hard as you can. Nothing will move, but it is measuring how hard you are squeezing."

Notes to examiner: Give vocal encouragement. Record the two trials (kgs) in column and score (ex: if testing a female and results are 10 and 8 kgs, record as 10/1.)

IX. HEAD LIFTED:
Patient preparation: The patient will lie down without a pillow under the head. A pillow may be placed under the knees or the knees bent so that the feet are flat on the bed.

Explanation to patient: "I need for you to lift your head off of the table. Keep it up as long as possible."

Notes to examiner: Place your hand under their head (without touching) to provide some cushion if the head drops back. The head should come up and forward, not just up to the ceiling. If the head drops within 10^{o} of neutral, stop the test.

X. RIGHT & LEFT LEG OUTSTRETCHED:
Patient preparation: Patient is supine with a pillow under the head. Both legs must be out straight and shoes off.

Explanation to patient: "I need for you to hold your right leg up. Hold the leg up in this position as long as possible."

Notes to examiner: Leg must be maintained at 45-50% of hip flexion. If the leg start to droop, ask the patient to lift the leg up. If the patient lifts the leg up, but cannot maintain that position for 2 seconds, stop the test. Watch for hands under the hips and/or rotation of the leg.

Myasthenia Gravis Foundation of America, Inc.

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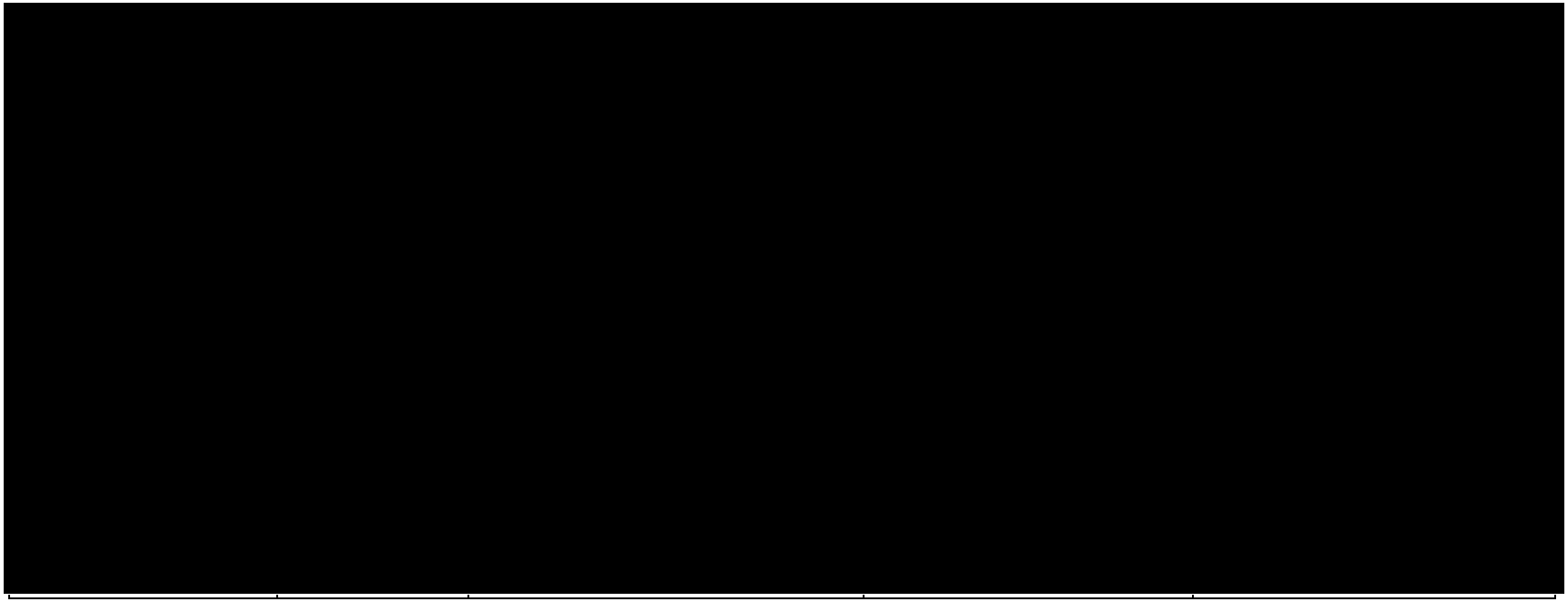
St Paul, MN 55104

Phone: (651) 917-6256 or (800) 541-5454
Fax: (651) 917-1835
Email: mgfa@myasthenia.org
Website: www.myasthenia.org

14.3 Appendix 3: Myasthenia Gravis Composite Score



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”.

Total Score

14.4 Appendix 4: The 15-Item Quality of Life Scale for Myasthenia Gravis

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
[redacted]			

MG-QOL15r total

14.5 Appendix 5: Clinical Laboratory Evaluations

Hematology	Complete blood count (CBC), [hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils)] and erythrocyte sedimentation rate (ESR).
Clinical Chemistry	Creatinine, creatinine clearance, blood urea nitrogen (BUN), glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase, lactate dehydrogenase (LDH), uric acid, albumin, potassium, sodium, calcium. thyroglobulin, International normalized ratio or activated partial thromboplastin time (aPTT), CD19 counts.
Urinalysis	Color, clarity/appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination including RBC, WBC, cast crystals, bacteria.
Serology	Hepatitis B virus (HBV) Hepatitis B surface antigen (HBsAg)], HBV core antibody, [hepatitis C virus (HCV), hepatitis C virus antibody (HCV-Ab)], human immunodeficiency virus (HIV) antibodies (1 and 2), and tuberculosis serology
Other	Serum and urine human chorionic gonadotrophin (ß-HCG), Follicle-stimulating hormone (FSH) test, and QuantiFERON®-TB Gold test.
Other Immunoglobulins*	IgA, IgD, IgE, and IgM.
Pharmacodynamic Parameters and PK Analysis*	Total IgG and IgG subtypes (IgG 1, IgG 2, IgG 3, and IgG 4) and anti-AChR antibodies that include anti-AChR binding antibodies and anti-AChR blocking antibodies.
Anti-drug antibodies (ADA)	Levels of anti-ARGX113 antibodies

*PK sample analysis, sample analysis for PD (assessing total IgG, IgG subtypes and other Immunoglobulins and Anti-AChR antibodies) and analysis for anti-drug antibodies (ADA) will be performed at SGS Cephac Europe SAS, and Q2 Solutions will manage the PK-PD-ADA samples and ship them for testing at SGS Cephac Europe SAS. All other laboratory tests such as hematology, clinical chemistry, urinalysis, and serology will be performed by Q2 Solutions.

14.6 Appendix 6: Sample Size

Assuming MG-ADL scores as a key indicator for efficacy. To detect the difference of 4 points between MG-ADL scores of Active and Placebo with variability [(1)] SD=1.80 for active and SD=3.72 for placebo, a sample size of 10 subjects per group would be sufficient to achieve 80% power. Approximately 36 patients will be screened in order to randomize approximately 24 patients (12 patients per treatment arm) to get at least 20 patients who received at least 3 doses of IMP (either ARGX-113 or placebo) and who completed at least 2 weeks of follow-up post last dose. Based on below calculation data of 10 to 12 subjects per group would be sufficient to produce clinically meaningful data for further exploratory analysis. Although this study is exploratory and not statistically powered, descriptive efficacy assessments will be analyzed to assist in designing future studies.

nQuery output:

Two group Satterthwaite t-test of equal means (unequal variances) (equal n's)

	1	2
Test significance level, α	0.050	0.050
1 or 2 sided test?	2	2
Group 1 mean, μ_1	4.300	4.000
Group 2 mean, μ_2	7.900	8.000
Difference in means, $\mu_1 - \mu_2$	-3.600	-4.000
Group 1 standard deviation, σ_1	1.800	1.800
Group 2 standard deviation, σ_2	3.720	3.720
Power (%)	80	80
n per group	12	10

Reference: Howard JF, Barohn RJ, Cutter GR, Freimer M, Juel VC et al. A Randomized, Double-Blind, Placebo-Controlled Phase II Study of Eculizumab in Patients with Refractory Generalized Myasthenia Gravis. Muscle & Nerve. 2013 Jul; 48 (1): 76-84.