STATISTICAL ANALYSIS PLAN

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

Protocol:	ARGX-113-1704
SGS LS number:	BE-80-1801534
Development phase:	Phase 3
Sponsor:	Argenx
Analysis purpose:	Final analysis
SAP version number:	Final 2.0.
SAP version date:	08MAY2020

SIGNATURE PAGE

Name and function	Date (ddMMMyyyy)	Signature
SGS LS author(s) and reviewer(s):		
PPD		
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Sponsor's approval: The approver agrees the statistical analysis will be performed according to this statistical analysis plan.		
PPD		
PPD		

PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final	15JUN2018	NAP
Final 2.0	28NOV2018	NAP
Final 3.0	11JUL2019	NAP

Protocol amendments:		
Version or ID	**Date (ddMMMyyyy)**	**Applicable country of the amendment**
Amendment 1.1	04DEC2018	UK specific amendment
Amendment 1.1	18JAN2019	Czech Republic specific amendment
Amendment 2.1	14MAR2019	UK and Czech Republic specific amendment
Amendment 1.1	28SEP2018	Japan specific amendment
Amendment 1.2	22OCT2018	Japan specific amendment
Amendment 1.3	03DEC2018	Japan specific amendment
Amendment 2.1	02JAN2019	Japan specific amendment
Amendment 2.1	08FEB2019	The Netherlands specific amendment
Amendment 2.2	25MAR2019	The Netherlands specific amendment
Amendment 3.1	01AUG2019	UK and Czech Republic specific amendment
Amendment 3.1	11JUL2019	Japan and The Netherlands specific amendment
Amendment 3.2	06NOV2019	Japan specific amendment

This statistical analysis plan (SAP) only considers the last version of the protocol, and of the protocol amendments, as listed above.

LIST OF ABBREVIATIONS

Ab	Antibody
AChE	Acetylcholinesterase
AChR	Acetylcholine receptor
ADA	Anti-drug Antibodies
ADaM	analysis data model
AE	adverse event
AESI	adverse events of special interest
ALQ	above the limit of quantification
ANCOVA	Analysis of covariance
BLQ	below the limit of quantification
bpm	beats per minute
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed plasma concentration
C_nB	cycle baseline for cycle n
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	diastolic blood pressure
DSMB	data safety monitoring board
DY	relative day
ADYP	ADaM variable to indicate relative day in period
ADY	ADaM variable to indicate relative day in study
ECG	electrocardiogram
EDC	electronic data capture
EoS	End of Study
EoT	End of Treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
eGFR	estimated glomerular filtration rate
FSH	Follicle-Stimulating Hormone
FU	Follow-up

gMG	Generalized myasthenia gravis
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobin G
IMP	Investigational medicinal product
IRR	Infusion-related reactions
ITC	Inter treatment cycle
ITT	Intent-To-Treat
mITT	Modified Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	myasthenia gravis activities of daily living
MGC	myasthenia gravis composite
MG-QoL15r	15-item Quality of life scale for Myasthenia Gravis [revised version]
NAb	Neutralizing Antibody
NAP	not applicable
NSID	Non-steroidal immunosuppressive drug
PD	pharmacodynamics
PK	pharmacokinetics
QMG	quantitative myasthenia gravis
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
SAP	statistical analysis plan
SAF	safety analysis set
SBP	systolic blood pressure
SCR	all screened subjects analysis set
SD	standard deviation
SE	standard error
SEB	study entry baseline
SGS LS	SGS Life Sciences

SoC	standard of care
SOP	standard operating procedure
STAT	statistics
TC_nB	treatment cycle baseline for cycle n
TEAE	treatment-emergent adverse event
UN	Unstructured covariance structure
VS	vital signs
WHO	World Health Organisation
WI	work instruction

DEFINITION OF TERMS

AChR-Ab seronegative patients	AChR-Ab seronegative patients refers to patients in whom the anti-AChR-Ab cannot be detected as stratified
case report form (CRF)	A printed, optical, or electronic document in which protocol required information is recorded for each trial subject.
display	Analysis table, figure or listing
phase	Interval of time in the planned conduct of a study that is associated with a specific purpose: for example, screening, treatment, follow-up.
study drug	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.
treatment-emergent abnormality	Any post-baseline abnormality that was not present at baseline (e.g. haemoglobin normal at baseline and grade 1 post-baseline; glucose low at baseline and high post-baseline; QTcF]450; 480] ms at baseline and >500 ms post-baseline)

TABLE OF CONTENTS

1. INTRODUCTION

This SAP describes the statistical analysis to be performed on the data from the ARGX-113-1704 (BE-80-1801534) study.

This SAP covers the final statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The statistical analysis will process and present the results following the International Council for Harmonisation (ICH) standards, in particular the ICH-E3, ICH-E6, and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

According to the protocol, the primary objective of this study is:

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

According to the protocol, the secondary objectives of this study are:

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

According to the protocol, the tertiary objective of this study is:

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

1.2 STUDY DESIGN

Study ARGX-113-1704 is a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial designed to evaluate the efficacy, safety, tolerability of

efgartigimod in patients with generalized myasthenia gravis (gMG) as well as the impact of efgartigimod treatment to affect patient quality of life and ability to perform normal daily activities . Patients are randomized in a 1:1 ratio to receive efgartigimod IV 10 mg/kg or placebo.

The trial duration is 26 weeks, which consists of:

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

The trial includes patients who are receiving SoC treatment for MG at a stable dose and regimen and who have a total MG-ADL score of ≥ 5 points at Screening and Baseline, with more than 50% of the total score attributed to non-ocular symptoms.

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

The schedules of assessments are in appendix 9.4.

TREATMENT CYCLES AND BASELINES

The trial includes a Screening period (pre-randomization) of approximately 2 weeks, a first Treatment Cycle, and a variable number of subsequent Treatment Cycles that are administered on an "as needed basis". Each Treatment Cycle comprises 9 weekly visits over an 8-week period, consisting of a 3-week Treatment period of 4 weekly infusions and a 5-week Follow-up (FU) period. Baseline at study entry (SEB) and the (first) Cycle ($C_{[1]}B$) are assigned as the date of randomization (i.e., Visit 1). The Baseline of each subsequent Cycle (C_nB) will be set at Visit 1 of the corresponding Cycle.

SCREENING AND TREATMENT

Patient eligibility for trial participation is evaluated during the Screening period.

Eligible patients receive blinded study drug in 4 weekly infusions during the Treatment Cycles in addition to their SoC. Study drug includes 4 weekly infusions of either efgartigimod IV 10 mg/kg or placebo, which is administered at Visit 1, Visit 2, Visit 3, and Visit 4 of the corresponding Treatment Cycle.

STANDARD OF CARE (SoC)

Patients should be receiving SoC at a stable dose and frequency prior to Screening. Protocol-permitted SoC for MG include non-steroidal immunosuppressive drugs (NSIDs) (e.g., azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide), steroids, as well as AChE inhibitors. In case these medications are taken for another indication than MG, same conditions apply.

A change in the SoC type or dose/regimen (e.g., replacement or removal of, addition to, or adjustment to SoC dose and/or frequency) is not allowed during the entire trial duration. Following the recommendation of the Myasthenia Gravis Foundation of America Inc (MGFA) manual for the QMG assessment, patients were not to receive

AChE inhibitors for at least 12 hours before completing the QMG assessment]) (Barohn 2000) and this temporary interruption is not considered a change in SoC.

TIME BETWEEN TREATMENT CYCLES

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

RE-TREATMENT

A new Treatment Cycle begins when all of the following criteria are met:

- The patient completed the previous Treatment Cycle (i.e. an 8-week time period after first dosing date) AND
- The patient has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms AND
- The Treatment Cycle can start at the latest on Day 127 or 7th February 2020 (for Japan), whichever comes first, and can be completed within the timeframe of the trial (26 weeks) AND
- For a patient who is an MG-ADL responder at the previous Treatment Cycle and has lost the response.

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

However, patients may not receive re-treatment with Efgartigimod or placebo if, at the time of re-treatment, patients have clinical evidence of bacterial, viral or fungal disease, or any other significant disease which could confound the results of the trial or put patients at undue risk. Patients who are in need of an additional treatment but who are not eligible to receive re-treatment for reasons listed here will remain in the trial to receive appropriate alternative MG treatment. Re-treatment with IMP may be reconsidered at next time where conditions for re-treatment are met, providing that at least 4 weeks have passed after other MG treatments.

ROLL-OVER

At the EoS visit or at the latest by 6th April 2020 (for Japan), patients will be offered the option to roll-over into a long-term, single-arm, open-label extension study ARGX-113-1705 in which efgartigimod IV 10 mg/kg will be administered on an "as needed basis".

Patients requiring re-treatment but cannot complete a Treatment Cycle within the time frame of the ARGX-113-1704 trial (i.e., require re-treatment after Day 127 or 7th February 2020 (for Japan), whichever comes first), may roll over immediately to the follow-on trial to receive treatment with efgartigimod.

Patients who discontinue from trial ARGX-113-1704 are not eligible for study ARGX-113-1705.

Patients who discontinue early from randomized treatment for rescue or pregnancy reasons or for an (S)AE that might jeopardize the safety of the patient are not eligible for ARGX-113-1705.

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

RESCUE THERAPY

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

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

1.3 EXPECTED SAMPLE SIZE

Approximately 150 patients (including approximately 16 Japanese patients) will be stratified according to three stratification factors: Japanese vs. non-Japanese patients, AChR-Ab status (seropositive or seronegative) and SoC (patients on NSIDs vs. patients not on NSIDs); and randomized within each stratum to be treated with either placebo or Efgartigimod both on top of their current SoC. A maximum of 20% of AChR-Ab seronegative patients will be allowed in the trial.

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

1.4 RANDOMIZATION AND BLINDING

ARGX-113-1704 is a randomized, double-blind, placebo-controlled trial. Efgartigimod and placebo will be identical in physical appearance. The treatment that each patient receives will not be disclosed to the Investigator, investigational site

staff, patient, Sponsor, and the Sponsor's designated CRO. The trial will only be unblinded following the database lock, except in the situation of unblinding for safety reasons. In addition, to maintain the blinding, PK, PD and ADA data will not be disclosed before database lock and unblinding.

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

1.5 INTERIM ANALYSIS

Not applicable.

1.6 SOFTWARE

SAS version 9.4 or later will be used for programming. WinNonlin Phoenix 8.0 or later (Pharsight Corporation, Palo Alto, Ca, USA) will be used for calculation of PK parameters.

1.7 VALIDATION MODEL

SGS Life Sciences (SGS LS) – Clinical Research statistics (STAT) standard operating procedures (SOPs) and work instructions (WIs) as effective at the project start will be followed throughout the project, provided the applicable regulatory requirements are still met.

Analysis Data Model (ADaM) datasets (except Subject-level Analysis Dataset (ADSL), and Efficacy Analysis Dataset (ADQS, primary parameter part only)), analysis tables and listings will be validated according to model B: review by an independent person. ADaM dataset ADSL and ADQS (only primary parameter) and the primary analysis tables will be validated according to model C: review by an independent person and independent programming of the parameters indicated in this SAP CCI .

PK analysis will be validated according CCI

2. GENERAL METHODOLOGY

2.1 ANALYSIS SETS

2.1.1 Analysis sets

The following analysis sets will be considered in the statistical analysis:

All screened subjects set (SCR):	subjects who *signed an informed consent* to participate in this study
All randomized subjects set (ITT):	subjects who were *randomized* into this study
Modified Intent-to-Treat (mITT)	all randomized patients who have a baseline efficacy score for MG-ADL and at least one post-baseline MG-ADL score.
Per-Protocol (PP)	subset of mITT i.e. all randomized patients who have a baseline efficacy score for MG-ADL and at least one post-baseline MG-ADL score and who received at least 3 out of 4 infusions (in any order) during the first cycle and without a major protocol deviation.
Safety analysis set (SAF):	all patients who received at least one dose or part of a dose.
PK analysis set (PK)	Safety analysis set excluding placebo patients and including patients with at least one post dose PK measurement

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Randomized is defined as having a complete randomization date in the database or any information to confirm randomization.

The efficacy and PD analyses will be done on the mITT. Sensitivity analyses of primary and secondary efficacy endpoints will be done on the PP. General characteristics, safety and immunogenicity analyses (ADA, NAb) will be performed on the safety analysis set. PK analysis will be performed on the PK analysis set; PK data review report will further discuss the PK analysis inclusion and/or exclusion.

The AChR-Ab seropositive subset population is defined based on the stratification factor as randomized.

2.1.2 As planned versus as actual analysis

For analyses done on the SAF, the actual treatment the subject received will be considered. For analyses on the ITT, mITT, and PP, the planned treatment of the subject will be considered. In case of misdosing during one infusion, actual treatment will remain equal to planned treatment.

2.2 PHASES, PERIODS AND TIME POINTS

2.2.1 Phases and periods

All events and assessments will be allocated to phases and periods (see Table 1). Each period includes the treatment cycle (4 administrations of IMP followed by the 5 weeks 'follow up'), the inter-treatment cycle (ITC) visits and safety and disease severity follow-up visits if applicable. The length of the ITC is patient-specific and can differ between the different periods. All subjects will have at least 1 treatment cycle, with an anticipated decline in the number of subjects participating in treatment cycle 2 and cycle 3. The period including the treatment cycle x, inter-treatment cycle visits and safety and disease severity follow-up visits (if applicable) is referred to as 'Cycle x'.

Table 1: phase/period definition

Phase	Period	Start	End
Screening		Date of signing the informed consent form (ICF), with 00:00 added as time part.	First administration date/time in cycle 1 – 1 minute. For screening failures the study termination date will be used.
Treatment+ FU	Cycle 1	First administration date/time in cycle 1	First administration date/time in cycle 2 – 1 minute or if last cycle: date of study termination, with 23:59 added as time part
	Cycle 2	First administration date/time in cycle 2	First administration date/time in cycle 3 – 1 minute or if last cycle: date of study termination, with 23:59 added as time part
	Cycle 3	First administration date/time in cycle 3	Date of study termination, with 23:59 added as time part

Per definition, and for each subject, the first phase starts on the date of the earliest available ICF signature, and the last available period ends on the date of last contact.

AEs and concomitant medications will be allocated to phases and periods as described in sections 5.1.2 and 3.5.2 respectively. All other assessments will be allocated to phases and periods based on the assessment date/time.

In case of (partially) missing date/time fields, the visit label will be used to allocate to the correct phase and period. If this is not possible (unscheduled visits or visits on a turning point between phases or periods), assessments will be handled as follows:

- Treatment phase vs. screening phase: assessments will be allocated to the treatment phase unless the available parts of the assessments start or stop date (time) provide evidence for allocating to the screening phase.
- Multiple treatment periods: assessments will be allocated to the first possible cycle unless the available parts of the assessments start or stop date/time provide evidence the assessments did not occur during that period.

2.2.2 Baseline and change from baseline

Two baselines are defined:

- SEB: Study Entry Baseline i.e. last available value prior to first administration of the IMP in the first cycle.
- CnB: Cycle n Baseline i.e. last available value prior to first administration of the IMP in cycle n, with n=1, 2, 3.

For parameters related to questionnaires, the baseline is the last value before or at the day of first administration of the IMP, independent of the time of administration.

A change from baseline can be calculated from SEB or CnB. Note: SEB coincides with C1B. SEB will be considered baseline for analyses that assess across all cycles and the CnB will be used for analyses restricted to a specific cycle, n.

A change from baseline for safety parameters will be calculated from SEB only.

For efficacy and PD, a change from baseline can be calculated from SEB or CnB, according to the analysis.

Change from baseline at time point t = value at time point t – baseline value.

A percent change can be calculated from SEB or CnB, according to the analysis:

Percent change from baseline at time point t = (actual value at time point t -baseline value)*100/baseline value.

2.2.3 Relative day

Relative days in the study (ADY) will be calculated according to the following rule:

- Concerned date < reference date: ADY = concerned date – reference date
- Concerned date ≥ reference date: ADY = concerned date – reference date + 1

The reference date is the date of first administration of study drug of the first treatment cycle.

Relative days in the period (ADYP) will be calculated in the same way, but the reference date is the date of first administration of study drug in the specific period.

2.2.4 Analysis visits

All assessments, including unscheduled assessments, will be allocated to analysis windows. Tables and listings will present the analysis windows as defined below, not the CRF visits. Allocation of assessments will be done using their relative day in the period (see section 2.2.3).

Table 3: Analysis visits

Phase/Period	Analysis window	Target ADYP	Lower limit ADYP	Upper limit ADYP
Screening	Screening*	-14	-INF	1
Treatment + FU /Cycle n				
	C_nB*	1	-INF	1**
	Week 1	8	1**	11
	Week 2	15	12	18
	Week 3	22	19	25
	Week 4	29	26	32
	Week 5	36	33	39
	Week 6	43	40	46
	Week 7	50	47	53
	Week 8	57	54	63
	Week 10	71	64	77
	Week 10+2x	71 + (x*2*7)	71+ (x*2*7) - 7	71+ (x*2*7) + 6

*: As the interval of screening and TC_1B are overlapping, it may be that the same assessment will be attributed to both timepoints.

**: An assessment on day 1 will be attributed to CnB in case it is before the infusion, to Week 1 otherwise, unless the assessment is related to questionnaires for which time will not be considered and therefore be allocated to CnB.

CnB:Cycle baseline for cycle n

Inter treatment cycle visits and Safety and disease severity follow up visit will be slotted to the applicable cycle period and analysis window.

Baseline is defined in section 2.2.2.

For those patients who will start a 2nd and 3rd cycle, the last assessment in a cycle, prior to the infusion of the next cycle, will be allocated to the appropriate analysis visit within the cycle and will also be allocated as the TCB visit of the next cycle.

Per parameter and analysis window, the value closest to the target ADYP will be used in analysis tables, other values will only be listed. If more than one value is located at the same distance from the target, then the latest in time will be selected. The value latest in time will be identified using, in order of preference, the assessment time, the visit label or the group identifier (if applicable). Missing values are removed before the selection is made. For questionnaires, the date of the total score will be used to

select the value closest to the target date and the according items of the same assessments will be used for the analysis.

2.2.5 Worst-case

A worst-case analysis visit will be created for parameters for which abnormalities and/or toxicity grades are defined to summarize values considered as the worst-case. For abnormalities it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a subject can have two worst-case analysis visits for a same parameter. For toxicity grades the worst-case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (hypo / hyper).

All non-missing post-baseline values, including unscheduled assessments will be considered when deriving the worst-case analysis visit.

2.3 IMPUTATION AND ROUNDING RULES

2.3.1 Missing values

For imputation on missing values related to efficacy, see appropriate section of the applicable efficacy endpoint.

2.3.2 Values below or above a threshold

Safety and PD values expressed as below the detection limit will be imputed by the value of the detection limit itself. PD values above the detection limit will be excluded from the analysis. Listings will always show the non-imputed values.

PK concentrations below the detection limit will be flagged as Below the Limit of Quantification (BLQ) in the listings. For PK parameter estimation, BLQ values will be set to zero at pre-dose and to missing in all other cases. For descriptive statistical analysis, all BLQ values will be set to zero. For ALQ values, all ALQ values will be set to the upper limit of quantification for descriptive analysis. Listings will always present the original value.

2.3.3 Rounding of derived variables

Derived variables will be rounded to the appropriate number of decimals at display level:

- Time since diagnosis will be rounded to 1 decimal.
- Estimated glomerular filtration rate (eGRF) will be rounded to 2 decimals
- Ratios will be rounded to the number of decimals of the parameter with the least number of decimals.

2.3.4 Outliers

There will be no outlier detection. All measured values will be included in the analyses.

For PK values, it will be decided whether extreme values are to be excluded from the analysis based on a detailed data review performed by SGS PK after the data base lock and before performing the PK analysis.

Clinical deviations that could affect the PK data of a subject, as well as the observed abnormal drug levels, sampling time deviations and their impact on PK population/analysis will be discussed with the sponsor during this data review process, to decide keeping or excluding data points/subjects from PK population/analysis.

The PK Data Review document, detailing such kind of decisions, will be agreed and signed by both parts before running the final PK analysis.

2.4 PRESENTATION OF RESULTS

All outputs described in this SAP will be repeated by region (Japanese / Non-Japanese) to support the J-MAA submission.

2.4.1 Calculation of descriptive statistics and percentages

In tables by analysis visit, only analysis visits with at least 10 subjects (overall) will be shown.

For continuous variables, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the median, minimum, Q1, Q3, maximum, and for efficacy the standard error (SE) and 95% CI may be provided in addition (see mocks for details).

Mean, Q1, Q3 and median will be presented with one more decimal place than the measured values. SE and SD will be presented with two more decimal places than the measured values. Minimum and maximum will be presented with the same number of decimal places as the measured values.

Descriptive statistics for PK concentrations will include n (number of observed values), arithmetic mean, standard deviation (SD), median, minimum and maximum, coefficient of variation (CV%).

Descriptive statistics for PK parameters will include n (number of observed values), arithmetic mean, standard deviation (SD), median, minimum and maximum, coefficient of variation (CV%) as well as geometric mean and geometric coefficient of variation.

Serum concentrations and PK parameters will be presented with 3 significant digits in the original concentration units, except values ≥ 1000 which will be presented without the decimals and t_{max} which will be presented with 2 decimals. The descriptive statistics should be rounded to the same number of significant digits as the individual values. If more than half of values are BLQ, SD, CV% and geometric coefficient of variation will not be calculated.

For event-type safety data, the number and percentage of subjects with an event will be shown. The denominator will be all subjects in the analysis set per treatment and phase or period. All periods will be shown, even if no events are present.

For frequency tabulations and cross-tabulations, the denominator will be all subjects in the analysis set per treatment. For tables where results are shown by analysis visit, the denominator will be all subjects in the analysis set per treatment and per analysis visit. Missing values will never be included in the denominator count when computing percentages. For cross-tabulations of post-baseline results versus baseline results, a 'missing' category will be shown for baseline results if applicable.

2.4.2 Presentation of treatments

The following treatment labels will be used in the tables and listings:

- efgartigimod
- placebo

In the general characteristics analysis, an overall total will be added to summarize all subjects over treatments. Overall totals will be shown last.

2.4.3 Ordering in tables and listings

All tables will be presented per treatment and period, unless specified otherwise. If present, worst-case will be shown last. The periods will be indicated like "Cycle x".

Listings for general characteristics will show results ordered by AChR-Ab status (As randomized), treatment and subject, unless specified otherwise.

All other listings will be ordered by AChR-Ab status (As randomized), treatment, subject, period, analysis visit and time point, unless specified otherwise.

In tables showing several parameters, each parameter will begin on a new page and parameters will be sorted alphabetically, within the parameter category if applicable.

AChR-Ab seropositive patients will be shown first, and then seronegative (as randomized). Efgartigimod treatment will always be shown first, and then Placebo.

The majority of tables are shown for the AChR-Ab seropositive population (as randomized) and overall. The table on AChR-Ab seropositive population will be shown first.

3. GENERAL CHARACTERISTICS ANALYSES

3.1 SUBJECT DISPOSITION

The following subject data will be tabulated:

- The number of subjects in each analysis set
- The number and percentage of subjects by country and site
- The number and percentage of subjects for each period/analysis visit.
- Descriptive statistics and tabulation in weeks of the period duration (see section 2.2.1), calculated as period end date – period start date + 1 day
- The number and percentage of subjects who completed or discontinued the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason.
- The number and percentage of subjects who completed or discontinued the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason by Cycle.
- The number and percentage of subjects who completed or discontinued the treatment as documented on the end of treatment page and the number and percentage of subjects for each treatment discontinuation reason.
- The number and percentage of subjects who completed or discontinued the treatment as documented on the end of treatment page and the number and percentage of subjects for each treatment discontinuation reason by Cycle.
- The number and percentage of subjects who roll over to study ARGX-113-1705.

All information collected in the CRF concerning treatment allocation, treatment discontinuation and study discontinuation will be listed. A listing with all COVID-19 related comments will also be prepared.

3.2 PROTOCOL DEVIATIONS AND ELIGIBILITY

The number and percentage of subjects with major protocol deviations will be tabulated, overall and per class of deviation.

All available information concerning major protocol deviations, violations on eligibility criteria and subjects not treated will be listed.

3.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

3.3.1 Available data

The following parameters will be available:

- Demographics: sex at birth, age at informed consent, race, Japanese/non-Japanese patients (as stratified and actual), height, weight at screening, body mass index at screening, year of birth, date of signing informed consent form (ICF).
- Baseline disease characteristics: date of diagnosis, MGFA Classification at screening, receiving NSID as SoC (as stratified and actual) (yes/no), thymectomy performed for MG (yes/no), time since thymectomy, AChR-Ab status (as stratified and actual), MG-ADL questionnaire (Total MG ADL Score), QMG questionnaire (Total QMG Score), MGC questionnaire (Total MGC Score), MGQoL15 questionnaire, (Total MGQoL15 Score), EQ-VAS, any emergency room visit for MG, any overnight stay in the hospital for MG, any intensive care visit for MG, regular use of a breathing mask, any use of feeding tube for MG and MuSK-Ab status.

3.3.2 Derivation rules

The following parameters will be derived:

- Japanese vs non-Japanese patients (including Hispanic or Latino, Not Hispanic or Latino and Not allowed to ask per local regulations)
- Standard of Care (SoC) (actual value): NSIDs vs. no NSIDs, (see eCRF FATESTCD=NSIDSOC)
- AChR-Ab status (actual value): based on lab value at screening (using a validated radioimmunoassay detection method) and using the normal ranges (within normal ranges is negative, outside is positive)
- MuSK-Ab status: based on lab value at screening will be derived using the normal ranges (within normal ranges is negative, outside is positive)
- Region (subgroup): country will be categorized into the following regions: Japan / USA / rest of the world
- Baseline MG-ADL score: 5-7, 8-9, ≥10
- Time since diagnosis/thymectomy (years): (date of ICF – date of diagnosis/thymectomy)/365.25. Partially missing date of diagnosis/thymectomy will be imputed as follows:
  - Missing day of diagnosis/thymectomy will be imputed with 1
  - Missing day and month of diagnosis/thymectomy will be imputed with 1JAN

  Note: Result will be rounded as detailed in section 2.3.3.

3.3.3 Presentation of results

Demographics will be presented using descriptive statistics for age, height, weight and BMI and frequency tabulations for age category, sex at birth, race, ethnicity, region, Japanese/non-Japanese patients.

Following age categories will be shown: 18-<65, ≥65 years.

Baseline disease characteristics will be presented using descriptive statistics for:

- time since diagnosis (years)
- time since thymectomy (years)
- total MG-ADL score
- total QMG score
- total MGC score
- total MGQoL15r score
- EQ-VAS

Baseline disease characteristics will be presented using frequency tabulations for

- MGFA Classification (at screening)
- AChR-Ab status (as stratified and actual)
- Standard of Care (SoC) (as stratified and actual)
- Thymectomy performed for MG
- Any emergency room visit for MG
- Any overnight stay in the hospital for MG
- Any intensive care visit for MG
- Regular use of a breathing mask
- Any use of feeding tube for MG
- MuSK-Ab status

All demographic data and baseline disease characteristics will be listed.

3.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

3.4.1 Available data

Medical history findings are coded using the medical dictionary for regulatory activities (MedDRA version 23.0) into system organ classes and preferred terms. For each finding, a start and stop date or ongoing flag is collected.

3.4.2 Derivation rules

Medical history finding: not ongoing at screening, ended before date of signing informed consent. Concomitant diseases are still ongoing at screening.

3.4.3 Presentation of results

Medical history (not ongoing at screening) and concomitant diseases (still ongoing at screening) will be tabulated in a separate table. The table will show:

- The number and percentage of subjects with findings
- The number and percentage of subjects with findings by system organ class and preferred term

All medical history and concomitant disease data will be listed.

3.5 PRIOR AND CONCOMITANT THERAPIES

3.5.1 Available data

All therapies are coded using the March 2020 version of the WHO-DRUG. ATC selection is performed. ATC coding up to level 4 is available in the clinical database. For each therapy, a start date or prior flag and stop date or ongoing flag are collected.

3.5.2 Derivation rules

Based on their start and stop date, therapies will be allocated to each phase and period during which they were administered. A therapy can therefore be reported in more than one phase or period.

Phases and periods are defined in section 2.2. Therapies with (partially) missing dates will be allocated to each phase/period unless the available parts of the therapy start or stop date or prior and ongoing flags provide evidence the therapy was not taken during that phase/period.

All therapies will be allocated into one or both of the following categories:

- Prior: the therapy strictly started before the first dose date
- Concomitant: the therapy was taken on or after the first dose date.

A medication that started before the first dose date and continued during the study will be classified as both prior and concomitant.

Additionally, prior MG-specific therapies will be allocated to one of the following categories:

- MG therapy stopped prior to screening
- MG therapy during Screening period: MG therapy taken between ICF and first dose date
- Prior MG therapy: MG therapy started before the first dose date

3.5.3 Presentation of results

Prior and concomitant therapies will be tabulated (separately), by ATC class (level 1 and level 3) and generic term. Table for prior concomitant therapies will exclude MG therapies. Table for concomitant therapies will include MG therapies.

All prior and concomitant therapies data will be listed with detailed information about ATC classes. Prior and concomitant procedures will be listed separately.

Summary tables on prior and concomitant medications will be provided overall, not by cycle.

Separate tables will be created for MG-specific therapies. These tables will also show the number of patients with at least 1 MG therapy, the number of patients with at least 2 MG therapies and the number of patients with at least 3 MG therapies. For MG therapies during the screening period, also the number of patients per medication class (Steroids, NSID's, AChE inhibitors: see appendix 9.3) and the combination of classes will be shown.

A separate listing will be created of patients receiving rescue medications. Rescue medications will be identified based on a flag on the SDTM data in the CM domain (Concomitant Medications).

3.6 STUDY DRUG ADMINISTRATION

3.6.1 Available data

For each study drug administration, the start and end date/times and the volumes will be recorded.

3.6.2 Derivation rules

The following parameters will be derived:

- Number of administrations: number and percentage of patients who had 1, 2, 3 etc.… administrations per treatment cycle and overall
- Actual dose (mg/kg) per administration per cycle, using categories <9mg/kg, 9-11 mg/kg, >11mg/kg.
- Treatment compliance per cycle defined as (number of doses received/4)*100%
- The actual dose in mg/kg will be calculated as = $\left(\frac{\text{actual volume extracted from vials (mL)} * 20\ (\text{mg/mL})}{\text{actual volume extracted from vials (mL)} + \text{actual volume of NaCl solution added to IV bag (mL)}}\right) * \left(\frac{\text{actual volume infused (mL)}}{\text{last available patient weight (kg)before or at day of dosing}}\right)$

  Note: As per protocol a variation of ± 10% of the amount of 10 mg/kg, will not be considered an overdose/underdose.

3.6.3 Presentation of results

A frequency table for the number of administrations per period and overall will be created.

Descriptive statistics of the overall number of administrations and treatment compliance.

All study drug administration data will be listed.

4. EFFICACY, PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

4.1 EFFICACY AND QUALITY OF LIFE

4.1.1 Available data

Efficacy will be assessed using MG-ADL, QMG, and MGC, and quality of life will be measured using 15-item Quality of life scale for Myasthenia Gravis [revised version] (MG-QoL15r) and EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L).

4.1.2 Endpoints and derivation rules

All efficacy endpoints will be analyzed on the overall mITT population and the AChR-Ab seropositive subset. For all references to weeks, analysis visits are considered as described in section 2.2.4 unless specified otherwise. If multiple assessments fall within the same analysis window, only the assessment closest to the target date based on the total score will be considered unless specified otherwise, other assessments within this window will only be listed and not considered in the below analyses.

In case of initiation of a new MG therapy or change in SoC therapy for any reason, assessments after receipt of a new MG therapy or after a change in SoC will be considered as:

- Having no reduction of at least 2 points (in case of total MG-ADL, or 3 points for QMG) at the applicable assessments to derive the response/non-response as defined in section 4.1.2.1
- Missing assessments for analysis on actual values and changes from baseline (descriptive stats, MMRM)

For PLEX and IVIg, the above rules only apply to the assessments obtained within 30 days of the PLEX/IVIg procedure.

4.1.2.1 PRIMARY ENDPOINT

The primary endpoint is the percentage of patients who, after the first cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in AChR-Ab seropositive patients.

A subject is considered as a responder if he/she shows a reduction of total MG-ADL of at least 2 points (compared to C1B) at response onset and for the next 4 consecutive visits (i.e. 4 consecutive weeks) after onset (see section 2.2.4) with the first of these decreases occurring at the latest 1 week after the last infusion. MG-ADL total score will be used as collected, no recalculation will be done.

This response is further referred to as "MG-ADL responder" in tables and listings.

Missing data will be handled as follows.

In general, the main reasons for missing data (i.e. due to missing visit or missing value(s) on specific questions) on an efficacy scale can be classified as:

a) Missing data due to MG disease worsening or missing data due to an AE;

b) Missing data not due to MG disease worsening (e.g. vacation) or an AE;

c) Missing data in analysis window as visit was performed out of window;

d) Missing data due to a missing value(s) on an efficacy scale (due to technical reasons, patient not able to perform the test with reason not linked to MG disease status, missing answer to a question, etc.).

Reason a) results in data missing not at random whereas reasons b), c) and d) can reasonably be considered as data missing at random.

The following rules are therefore intended for the handling of missing visit or missing values:

- Patients who drop-out or are lost-to-follow-up will be treated as non-response, in case they have not achieved a MG-ADL response before.
- Intermittent missing data at only 1 of 4 post-onset (O) consecutive analysis windows: if the missing data follows one of the following score patterns: OXmXX, OmXXX, OXXXmX or OXXmX then the patient will be considered as having achieved a MG-ADL response providing that the missing data 'm' is not due to reason a). If no such pattern is present the patient will be considered as not having achieved a MG-ADL response.
- Intermittent missing data following onset of response at ≥ 2 of 4 consecutive post-onset analysis windows: regardless of the reason for missing data, the patient will be considered as not having achieved a sustained response.

Missing data at one or more consecutive analysis windows after onset of response

Reason for missingness	Score change pattern	Interpretation (binary response)
Missing visit due to a worsening of the disease or an AE	NA	Non-responder
Missing visit NOT due to a worsening of the disease or an AE	OXmXX or OXXmX, OmXXX, OXXXmX	Responder
	mOXXX, OXXXmY*	Non-responder
Missing data ≥ 2 of 4 consecutive visits after onset of response	NA	Non-responder

m = missing value; X=decrease of at least 2 points on the total MG-ADL score; Y= increase or decrease of less than 2 points in MG-ADL; O=onset of decrease of at least 2 points on the total MG-ADL score; * A sequence of non-response will be overruled if a subject also fulfils the criteria of being a responder with onset at any time at or before 1 week after the last infusion of the IMP.

4.1.2.2 SECONDARY ENDPOINTS

The following 5 secondary endpoints are defined:

1) Percentage of patients who, after the first cycle, have a decrease of at least 3 points on the total QMG score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion in AChR-Ab seropositive patients.

The same derivation rules as the primary efficacy endpoint (see section 4.1.2.1) apply, including handling of missing data.

2) Percentage of patients who, after the first cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP group in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

The same derivation rules as the primary efficacy endpoint (see section 4.1.2.1) apply, including handling of missing data.

3) Percentage of time that patients have a "clinically meaningful improvement" in total MG-ADL score compared to SEB during the study (up to and including Day 126) in AChR-Ab seropositive patients.

Percentage of time that patients show a clinically meaningful improvement in MG-ADL score is calculated per patient as follows:

- Day 1 is the day of first treatment in cycle 1
- All assessments will be used up to and including Day 126
- Calculate the number of days each patient has a decrease in total MG-ADL score from SEB ≥2 points.
- A period of clinically meaningful improvement starts with the first visit with a decrease in total MG-ADL score from SEB ≥2 points
- Clinically meaningful improvement continues as long as a decrease in total MG-ADL score from SEB ≥2 is observed at subsequent visits.
- Missing values will be handled as follows.
    - If a missing value is due to an AE or worsening of disease, the clinically meaningful improvement will end at the day before the theoretical visit date.
    - In case of an intermittent missing value for other reasons than AE or worsening of disease between 2 clinically meaningful improvement visits (XmX), then the patient continues his period of improvement.
    - In case an intermittent missing value is followed by drop less than 2 in MG-ADL or another missing visit, the period of clinically meaningful improvement ends on the day before the theoretical visit date of the first missing value.

- If a patient has more than one separate period of clinically meaningful improvement (of total MG-ADL score decrease from SEB ≥2) these periods will be summed and then divided by 126 in case the patient is still ongoing at Day 126.
- In case of initiation of a new MG therapy or change in SoC therapy or use of PLEX/IVIg subsequent assessment will be handled as mentioned in section 4.1.2
- In case of study discontinuation, the patient will be considered as having no reduction of at least 2 points the day after his/her last total MG-ADL score
- In case the patient is ongoing at Day 126, the last clinically meaningful improvement status before Day 126 will be carried forward up to Day 126.
- Japanese patients who roll-over to 1705 before Day 126 (as allowed per protocol amendment) will use as denominator: study termination date-first dose date +1

4) Time from Week 4 to qualification for re-treatment, as assessed by monitoring the total MG-ADL score (compared to C1B), in the AChR-Ab seropositive patients.

Time to qualification for re-treatment will be calculated as the first assessment where the below 2 criteria are met:

- The patient has a total MG-ADL score of ≥ 5 points with more than 50% of the total score due to non-ocular symptoms, and
- No clinically meaningful improvement (decrease in total MG-ADL score from C1B <2)

Time to qualification of re-treatment: Date (first assessment) – Date (Week 4) + 1.

In case the Week 4 visit is missing the target date of this visit will be used instead.

All observed data after Week 4 will be considered, not only the assessments closest to the target date.

In case of initiation of a new MG therapy or change in SoC therapy or use of PLEX/IVIg or discontinued due to an AE before week 4, the patient will be considered as having an event at time 1.

A patient which starts a new cycle before qualification for re-treatment, will be censored at the date of first IMP use of the new cycle.

If the patient discontinued due to other reasons before week 4, he/she will be censored at time 1.

A patient who initiates a new MG therapy or changes SoC therapy or uses of PLEX/IVIg or discontinues the trial at or after week 4 and before reaching the condition for ‘qualification for re-treatment’, will have an event at the time of initiation of MG therapy/PLEX/IVIg or change in SoC.

In case of discontinuation and not yet qualified for re-treatment, the patient will have an event the day after his/her last total MG-ADL score.

A patient who completes the study and does not reach the condition for ‘qualification for re-treatment’ will be censored at his/her last total MG-ADL score.

5) Percentage of patients who, after the first cycle, have a decrease of at least 2 points on the total MG-ADL score (compared to C1B) for at least 4 consecutive weeks with the first of these decreases occurring at the latest after 1 or maximum 2 infusions of IMP (early MG-ADL responders) in the AChR-Ab seropositive patients. In practice, visit 'Week 2' is the last visit the onset of response can start, to be considered an early responder, even in case of a missed infusion.

The same derivation rules as for the primary efficacy endpoint (see section 4.1.2.1) apply, including handling of missing data.

This response is further referred to as "Early MG-ADL response".

4.1.2.3 TERTIARY ENDPOINTS

The following 5 tertiary endpoints are defined:

1) Percentage of patients who, from the second cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding cycle baseline) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in this cycle in AChR-Ab seropositive patients.

2) Percentage of patients who, from the second cycle on, have a decrease of at least 3 points on the total QMG score (compared to each corresponding cycle baseline) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after the last infusion of the IMP in this cycle in AChR-Ab seropositive patients.

3) Percentage of patients who, from the second cycle on, have a decrease of at least 2 points on the total MG-ADL score (compared to each corresponding cycle baseline) for at least 4 consecutive weeks with the first of these decreases occurring at the latest 1 week after last infusion of the IMP in this cycle in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

4) Percentage of time that patients have a “clinically meaningful improvement” in total MG-ADL score compared to SEB during the study (up to and including Day 126) in the overall population (AChR-Ab seropositive and AChR-Ab seronegative patients).

5) Change from Baseline -SEB and CnB- (Visit 1) in total MG-QoL15r score.

The same derivation rules apply as for the primary and secondary endpoints.

4.1.2.4 EXPLORATORY ENDPOINTS

Following exploratory endpoints are defined:

1) Characterization of response in MG-ADL per cycle:

- Onset (First drop of >=2 MG-ADL in sequence of 4 week/5 assessments)
- Duration of response (in days) and categorized in Weeks
- Magnitude of response (maximum drop from cycle baseline)
- Minimum MG-ADL value within the duration of response
- Percentage of early responders

Only visits closest to the target date will be used for the calculation of duration of response expressed in days. A response continues as long as a response is observed at subsequent visits and ends the day before a non-response is observed. If a patient is still in response at end of study or at the time of roll-over, the last available assessment will be used to calculate the duration. For categorization in weeks the window of week x starts at relative day x*7-2 until x*7+4

Missing values will be handled as follows:

- If a missing value is due to an AE or worsening of disease, the response will end at the day before the theoretical visit date.
- In case of an intermittent missing value between 2 response visits (XmX), then the patient continues to be a responder.
- In case an intermittent missing value is followed by a non-response visit (drop less than 2 in MG-ADL) or another missing visit, the response ends on the day before the theoretical visit date of the first missing value.

Analysis will be done on AChR-Ab seropositive patients, AChR-Ab seronegative patients and overall but limited to the subset of patients with MG-ADL response.

2) Characterization of response in QMG per cycle:

The analysis is identical to the characterization of response in MG-ADL.

3) Characterization of clinically meaningful MG-ADL improvement (i.e. 1 drop of at least 2 in MG-ADL)

- Onset (First drop of >=2 MG-ADL)
- Duration of clinically meaningful improvement (in days) and categorized in Weeks
- Magnitude of clinically meaningful improvement (maximum drop from SEB)
- Minimum value within the duration of clinically meaningful improvement

Note: only the first clinically meaningful improvement period will be considered.

Missing values will be handled similar as is done for characterization of response in MG-ADL.

Analysis will be done on AChR-Ab seropositive patients, AChR-Ab seronegative patients and overall but limited to the subset of patients with clinically meaningful improvement.

4) Characterization of clinically meaningful QMG improvement (i.e. 1 drop of at least 3 in QMG total score) per cycle

The analysis is identical to the characterization of clinically meaningful MG-ADL improvement.

5) Overview of MG-ADL response/non-response for first and subsequent cycles

- XX% of patients were responders after first cycle, of which YY% were retreated and ZZ% of these patients responded to second cycle and so on
- XX% of patients were non-responders after first cycle, of which YY% were retreated and ZZ% of these patients responded to second cycle and so on

Analysis will be done on AChR-Ab seropositive patients and overall.

6) Actual values and change from baseline -SEB and CnB- in total MG-ADL score will be analysed descriptively and categorically.

Categories to be used for actual values in MG-ADL total score: 0, 1, 2, 3, 4, 5-7, 8-9, 10-12, 13-16, 17-20 and 21-24.

Categories to be used for changes from baseline in MG-ADL total score: >0, 0, -1, -2, -3, -4, -5, -6, -7, -8, -9, -10, <-10. Number of patients, percentages and cumulative percentages will be shown.

In addition to the planned timepoints, following timepoints will be shown for each cycle:

- Maximum drop from baseline – SEB and CnB – in MG-ADL
- Minimum post-baseline MG-ADL score

Missing data will not be considered.

Analysis will be done on AChR-Ab seropositive patients, AChR-Ab seronegative patients and overall.

The analysis will be repeated for the individual items of MG-ADL for the AChR-Ab seropositive patients and overall. For individual items the maximum drop from baseline and minimum score will not be shown.

7) Actual values and change from baseline -SEB and CnB- in total QMG score and the individual items will be described descriptively and categorically as for the MG-ADL score. Of note for the categorization of the QMG total score a category of ≥25 will be added.

8) Actual values and change from baseline -SEB and CnB- in total MGC score at each time point.

Analysis will be done on AChR-Ab seropositive patients and overall.

9) Frequency tabulation on EQ-5D-5L (i.e., mobility, self-care, usual activities, pain/discomfort, anxiety/depression) at each timepoint.

10) Change from Baseline -SEB and CnB- in EQ-VAS score to each time point.

Analysis will be done on AChR-Ab seropositive patients and overall.

4.1.3 Presentation of results and statistical analysis

Summary statistics will be provided in terms of absolute values and changes from baseline (SEB (overall) and CnB (for each cycle)) for continuous parameters in AChR-Ab seropositive patients, AChR-Ab seronegative patients (if applicable, see section 8.1 for details) and the overall mITT population.

Absolute values and changes from baseline (SEB (overall) and CnB (for each cycle)) will also be categorized, including the number of subjects within each category, the percentage and the cumulative percentage in AChR-Ab seropositive patients, AChR-Ab seronegative patients (if applicable, see section 8.1 for details) and the overall mITT population.

Frequency tabulations will be provided of the percentage of MG-ADL responders during the first cycle in AChR-Ab seropositive patients and overall and by stratification factors (Japanese, non-Japanese patients), SoC and AChR-Ab status. Similar tabulations will be provided for QMG responders on AChR-Ab seropositive patients and overall. The same frequency tabulations will be repeated for the subsequent cycles.

For the early MG-ADL responders, frequency tabulations will be provided by cycle in AChR-Ab seropositive patients and overall.

Inferential statistics are limited to the first cycle with the exception of MG-ADL and QMG response in cycle 2 and percentage of time of having a clinically meaningful improvement on total scores (MG-ADL) which will be done over the first 126 day period.

All statistical comparisons will be made using two-sided tests at the 0.05 significance level unless specifically stated otherwise.

The primary endpoint, treatment effect in MG-ADL response, is tested by means of a 2-sided exact test (using logistic regression) stratified for the stratification factors (Japanese/non-Japanese patients) and Standard of Care (SoC) and using the baseline total MG-ADL score as covariate at the 2-sided 5% significance level, in the AChR seropositive patients. The treatment effect will be presented as the odds ratio together with its 95% confidence interval (CI) and 2-sided p-value. An odds ratio of more than 1 represents a higher response rate for Efgartigimod compared to placebo.

To control the type I error for the primary and secondary endpoints, the primary efficacy endpoint will be tested at the 5% 2-sided alpha level and will act as gatekeeper for the testing of secondary endpoints. The primary endpoint and secondary endpoints will be tested in a strict hierarchical order as listed under section 4.1.2.1 and 4.1.2.2 to control the type I error. If a certain endpoint turns out be non-significant at the 5% significance level, subsequent endpoints will no longer be evaluated.

For response parameters during the first cycle related to MG-ADL and QMG a similar logistic regression model will be applied as for the primary efficacy endpoint with AChR-Ab status as additional stratification factor when the analysis relates to the overall population.

The endpoints on Percentage of time that patients have a “clinically meaningful improvement” will be analyzed using an ANCOVA model with treatment (as randomized) and baseline total score as a covariate; the model will be stratified for the stratification variables (Japanese/non-Japanese patients, SoC and AChR-Ab status if applicable).

The following statistics will be presented for an ANCOVA:

- Least Square (LS) Mean per treatment group;
- Standard error of LS Mean;
- 95% confidence interval (CI) of LS Mean;
- LS Mean Difference (Efgartigimod – placebo);
- Standard error of LS Mean Difference;
- 95% confidence interval (CI) for LS Mean Difference;
- 2-sided p-value for testing differences between treatment groups.

The 'Time to qualification for re-treatment monitored by total MG-ADL score (compared to C1B) will be analysed using Kaplan-Meier time to event analysis (stratified log-rank test), stratified for the stratification variables.

For the time to event analysis the following will be presented:

- Number and percentage of events;
- Number and percentage of censored observations;
- 25th percentile (95% CI);
- Median (95% CI);
- 75th percentile (95% CI);
- P-value (Efgartigimod vs. placebo) using stratified log-rank test.

Sensitivity analyses will be done for the primary and secondary endpoints on the Per-Protocol population. A second sensitivity analysis will be done for the primary endpoint on the mITT population by using a missing is failure imputation. This imputation will be applied for visits week 1 to week 8 where missing data will be considered as not having achieved a drop of 2 point in MG-ADL total score. After this imputation the response in MG-ADL will be derived.

The primary endpoint will also be repeated using the actual values of the stratification factors rather than the values as randomized.

The primary endpoint will also be analyzed using a Cochran-Mantel-Haenszel statistic stratified for the stratification factors (Japanese/non-Japanese patients) and Standard of Care (SoC)). The treatment effect will be presented as the odds ratio together with its 95% confidence interval (CI) and 2-sided p-value. Also an adjusted difference of the proportions with its 95% confidence and 2-sided p-value will be provided.

For MG-ADL response and QMG response, the number and percentage of responders will also be calculated for a subset of the AChR-Ab seronegative patients, defined as being AChR-Ab seronegative based on the screening central lab data and, based on historical data or for whom no historical information is available.

For total MG-ADL, QMG, MG-QoL15r and MGC score changes from baseline (C1B), between treatment group differences will be analyzed by means of Mixed Models for Repeated Measurements (MMRM). All available data up to week 8 will be included. The model will include treatment, visit and treatment by visit interaction

terms as fixed effects, with baseline value and stratification factors as covariates. Within-subject correlation will be modeled by assuming an unstructured covariance matrix for the error terms.

The same statistics will be presented for each visit as for the ANCOVA model.

If the model does not converge upon using UN, the following covariance structures will be tested for convergence (in order): toeph, arh(1), csh, toep, ar(1) and cs.

For MG-ADL and QMG response, following subgroups will be considered:

- Age category at baseline: 18-<65, ≥65 years
- Gender
- Race
- Region (US/Japan/ Rest of World (RoW))
- Baseline MG-ADL score: 5-7, 8-9, ≥10
- Number of cycles: 1, 2 or 3

For the above subgroups, response rates and differences in response rate (Efgartigimod-Placebo) will be shown together with the 95% Wald confidence limits.

For further details on the planned analyses tables and listings, see section 8.1.

4.2 PHARMACOKINETICS

4.2.1 Available data

Blood samples will be collected for the determination of efgartigimod concentration at the time points indicated in the schedule of assessment (Section 9.4).

Time windows for PK samples are specified as follows:

- Dosing days: within 1 hour prior to the start of infusion for the predose PK sample; within 1 hour after end of infusion for the postdose PK sample;
- Non-dosing days: +/-1 day;
- End of Study / Early Discontinuation: +/- 3 days.

All concentration data-points with deviations outside these permitted ranges will be excluded from the descriptive statistics on concentrations, explained by a footnote in the appropriate tables, but kept in PK parameters estimation.

4.2.2 Derivation rules

The PK analysis will be based on actual sampling times from start of IV infusion. Standard non-compartmental methods will be used for the calculation of the

following parameters from the individual serum drug concentrations versus time profile for Efgartigimod:

- C_{max}: maximum observed serum concentration per visit (Visit 1, 2, 3 and 4);
- C_{trough}: Serum concentration observed pre-dose at Visit 2, 3 and 4;
- AUC_{0-t}: the area under the serum concentration-time curve from 0 to the last quantifiable concentration will be computed using the linear trapezoidal rule (for the Japanese subjects on Visit 1 and 4);
- R_{ac}: accumulation ratio calculated as Visit 4 C_{max} /Visit 1 C_{max}.

The above PK parameters will be estimated for all applicable cycles.

For PK analysis, the following rules will be applied:

- Concentration below limit of quantification (BLQ) will be imputed according to the rules mentioned in section 2.3.2;
- Quantifiable Visit 1 predose values exceeding 5% of C_{max} will be flagged in the tables and excluded from the descriptive statistics calculation.

PK parameters that cannot be estimated will be specified in the PK Data Review document.

4.2.3 Presentation of results

All data issues with how the issue will be handled will be listed per subject and time point.

Individual concentration data and actual blood sampling times from start of IV infusion for PK assessments will be listed.

Descriptive statistics on concentration data will be presented in tables per cycle, per infusion within a cycle and per time point. Descriptive statistics will be calculated over all subjects and in addition, by randomization stratification factors: Japanese vs. non-Japanese patients, SoC and AChR-Ab status.

Individual PK parameters will be listed. Descriptive statistics on PK parameters will be presented in tables per cycle and per infusion within a cycle. Descriptive statistics will be calculated over all subjects and in addition, by randomization stratification factors: Japanese vs. non-Japanese patients, SoC and AChR-Ab status.

4.3 PHARMACODYNAMICS

4.3.1 Available data

The following pharmacodynamic parameters will be measured: PD markers (total IgG and IgG subtypes [IgG1, IgG2, IgG3 and IgG4], and autoantibodies (anti-AChR antibodies for the AChR-Ab seropositive patients and anti-MuSK antibodies for the MuSK-Ab seropositive patients).

4.3.2 Endpoint and derivation rules

1) Change and percent change (compared to Baseline -SEB and CnB) in total IgG level and IgG subtypes [IgG1, IgG2, IgG3 and IgG4] at each visit.

In addition to the planned timepoints, following timepoints will be shown for each cycle:

- Maximum drop from baseline – SEB and CnB
- Minimum post-baseline value

Analysis will be done on AChR-Ab seropositive patients and overall.

This analysis will also be done by Japanese vs. non-Japanese patients

2) Change and percent change (compared to Baseline -SEB and CnB) in anti-AChR antibodies (in AChR-Ab seropositive patients) and in anti-MuSK antibodies (in MuSK-Ab seropositive patients) at each visit.

In addition to the planned timepoints, following timepoints will be shown for each cycle:

- Maximum drop from baseline – SEB and CnB
- Minimum post-baseline value

See section 2.2.2 for calculation of change and percent change from baseline.

Values Below the limit of quantification (BLQ) will be imputed with the lower limit of quantification. Patients with a baseline value BLQ will be excluded from the statistical analysis and only be listed.

4.3.3 Presentation of results and statistical analysis

Summary statistics will be provided in terms of absolute values and changes from baseline (SEB and CnB) for each cycle and overall. Moreover, percent changes from baseline will also be presented.

For cycle 1, changes from baseline and percent changes from baseline between treatment groups at the different post-baseline time points will be analyzed by means of Mixed Models for Repeated Measurements (MMRM) (using all available data of cycle 1 up to Week 8) for total IgG, IgG subtypes and anti-AChR antibodies. The same model details as applicable for the tertiary endpoints' analysis on total MG-QoL15r score changes from TC1B (see section 4.1.3) are valid.

All data will be listed.

4.4 ANTI-DRUG ANTIBODIES

4.4.1 Available data

Presence of anti-drug antibodies (ADA) to efgartigimod is measured at TC1 Visits 1, 4, 6 and 9 and for subsequent cycles at Visit 1, 9 and EOS.

ADA samples are analyzed in a 3-tiered approach:

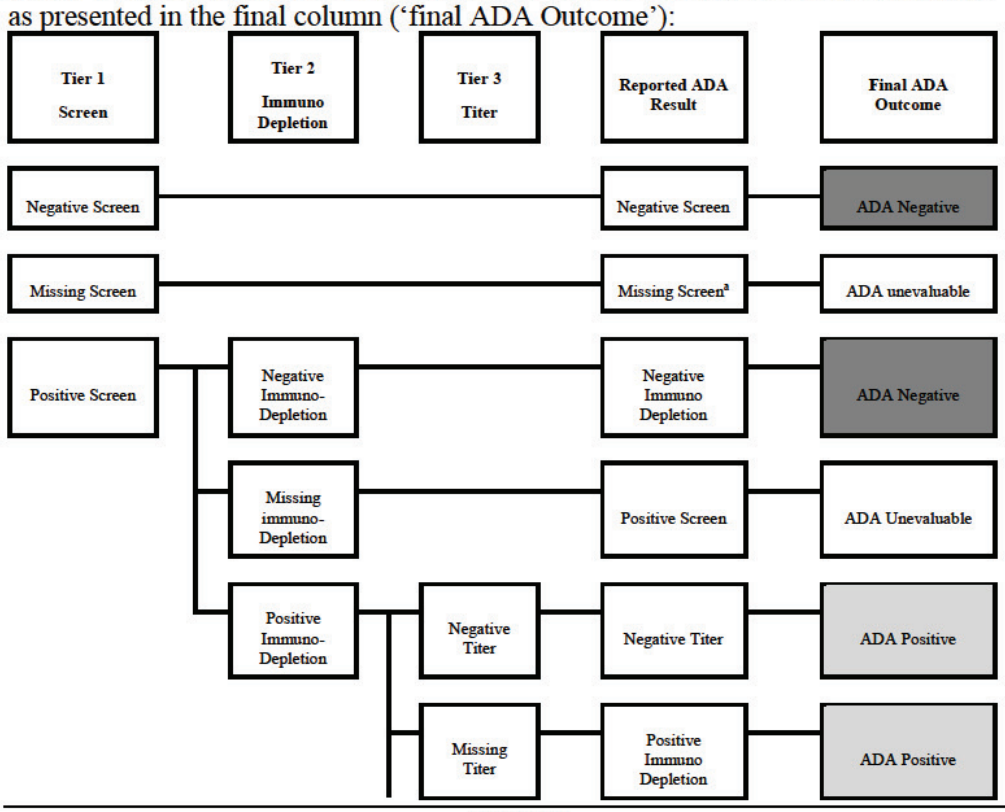
- All samples are evaluated in the ADA screening assay and are scored ADA screening positive or negative
- If a sample scored ADA screening positive, it is further evaluated in the confirmatory assay and is scored confirmed positive (positive immunodepletion) or confirmed negative (negative immunodepletion).
- If a sample is scored as confirmed positive, the samples are further characterized in the ADA titration assay (to determine titer) and are also further analyzed in the Nab assay to confirm neutralizing activity (positive or negative)

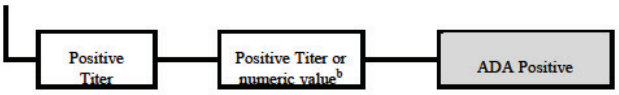
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

In case the ADA confirmed positive sample could not be run in the titration assay (e.g. due to insufficient sample volume/quality to perform the titer analysis) the result will be described as 'positive immunodepletion' and the sample should be considered as ADA positive.

If a sample is not reported or reported as 'positive screen', the ADA sample status is ADA unevaluable.

An overview of this 3-tiered approach and all possible ADA sample results that will be reported by the laboratory is given below. From these reported ADA sample results a final ADA sample status needs to be derived during the statistical analysis, as presented in the final column ('final ADA Outcome'):





[a] missing screen includes the following terms (reported as reason not done): NA (not analysed), NR (no result), NS (no sample) and SL (sample lost). More details can be found in the IS data transfer agreement from SGS France to SGS SD office.

[b] 'positive titer' is reported in case it was not possible to retrieve a numeric value.

4.4.2 Derivation rules

4.4.2.1 Subject Classification for ADA – Overall and by Cycle

Table below gives an overview of how the ADA subject classification will be derived, starting from the patient baseline ADA sample status.

Subject ADA classification	**Highest[c] post baseline[d] sample status**				
	ADA negative	**ADA positive (missing titer[a])**	**ADA positive (negative titer[b] or positive titer)**		**ADA not evaluable**
Baseline (SEB) ADA sample status					
ADA negative	ADA negative	Treatment Induced ADA	Treatment Induced ADA		*ADA unevaluable*
ADA positive (missing titer[a])	Treatment Unaffected ADA	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*
ADA positive (negative titer[b] or positive titer)	Treatment Unaffected ADA	*ADA unevaluable*	**titer < 4 x baseline titer:** Treatment Unaffected ADA	**titer ≥ 4x baseline titer:** Treatment Boosted ADA	*ADA unevaluable*
ADA not evaluable	*ADA unevaluable*	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*

[a] Samples with missing titer have as reported ADA result 'positive immunodepletion';
[b] Results reported as 'negative titer', i.e. titer value <1 will be set to value of 1;
[c] Highest sample status, with order: (from low to high): ADA unevaluable, ADA negative, ADA positive (positive immunodepletion), ADA positive with titer < 1 ('negative titer' as reported ADA result, titer value set to 1), ADA positive with titer ≥ 1 (i.e. positive titer and selecting the sample with highest titer)
[d] For the evaluation per cycle, the assessments within that cycle including all assessments before first dose of the next cycle.

Notes:

- Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (=two times the dilution factor) (reference to Shankar et al., 2014).
- Comparison is always relative to the study entry baseline, not to the cycle baseline.

ADA incidence=percentage of patients with treatment-induced or treatment-boosted ADAs (denominator: number of evaluable patients=patients with at least one post-baseline sample). Treatment-unaffected ADAs are not taken into account.

ADA prevalence=percentage of patients with treatment-unaffected ADA, treatment-induced ADA or treatment-boosted ADA.

4.4.2.2 SUBJECT CLASSIFICATION FOR NAB – OVERALL AND BY CYCLE

All ADA confirmed positive samples will also be evaluated in the NAb assay. All samples that were not analyzed in the NAb assay (i.e. the ADA negatives) are per default NAb negative. Samples with ADA status unevaluable should be classified as NAb unevaluable. Also, if a NAb sample is not reported, the NAb sample status is NAb unevaluable

All samples evaluated in the NAb assay will be scored as NAb positive, NAb negative or NAb unevaluable. Based on these results, the subjects will be categorized based on their baseline and post-baseline sample status as detailed in following table.

Subject NAb classification	**Highest[a] post baseline[b] NAb sample status**		
	NAb negative	**NAb positive**	**NAb not evaluable**
Baseline (SEB) Nab sample status			
NAb negative	baseline neg – post-baseline neg	baseline neg – post-baseline pos	*NAb unevaluable*
NAb positive	baseline pos - post-baseline neg	baseline pos – post-baseline pos	*NAb unevaluable*
NAb not evaluable	*NAb unevaluable*	*NAb unevaluable*	*NAb unevaluable*

a: Highest sample status in order: (from low to high): NAb unevaluable, NAb negative, NAb positive.
b: For the overall NAb subject classification, the highest post baseline sample status over all cycles is used for comparison with the baseline NAb sample status. For the cycle NAb subject classification, the highest post baseline sample status within the cycle is used for comparison with the baseline NAb sample status.

Note: Comparison is always relative to the study entry baseline, not to the cycle baseline.

NAb incidence=percentage of patients with subject classification 'baseline neg – post-baseline pos' and 'baseline pos – post-baseline pos' (denominator: number of evaluable patients=patients with at least one post-baseline sample).

NAb prevalence=percentage of patients with subject classification 'baseline neg – post-baseline pos', 'baseline pos – post-baseline pos' or 'baseline pos – post-baseline neg' (denominator: number of evaluable patients=patients with at least one post-baseline sample).

4.4.3 Presentation of results

Analysis will be done on AChR-Ab seropositive and the overall population.

Frequency tabulations (number and percentages) will be provided with ADA negative/positive/unevaluable samples per visit.

Frequency tabulations (number and percentages) will be provided by cycle and overall on:

- patients per ADA subject category
- prevalence and incidence of ADA
- ADA unevaluable patients
- ADA baseline positive/negative/unevaluable samples

For details on the definitions, see the above section 4.4.2.1.

The above frequency tabulations will be repeated for NAb assay using the definitions as defined in section 4.4.2.2.

In addition, a frequency tabulation (number and percentages) will be provided of NAb positive patients within the overall ADA subject category (Treatment-unaffected ADA, Treatment-induced ADA, and Treatment-boosted ADA).

Correlation tables (restricted to the Efgartigimod treated patients only) by ADA subject category per cycle will be provided for the following parameters:

- mean drug concentration over time
- mean percent change from baseline in total IgG
- number and percentage of MG-ADL responders in cycle 1
- number and percentage of QMG responders in cycle 1

The above tables will be repeated for NAb subject category as defined in previous section.

The NAb/ADA subject category of the applicable cycle will be used for all tables.

Individual patient profiles will be provided for patient with ADA positive samples (i.e., Treatment-unaffected, treatment-induced and treatment-boosted ADA).

A single page per patient will be foreseen including following information:

- Upper panel: ADA titer over time + NAb response (either Y/N at the respective time points)
- Mid panel: Individual PK and percent change from baseline in total IgG together with the population mean levels (dotted lines).
- Lower panel: Individual change in baseline in MG-ADL score and QMG score together with the mean population levels (dotted lines). In addition will the MG-ADL and QMG responder status be shown.

5. SAFETY ANALYSES

5.1 ADVERSE EVENTS

5.1.1 Available data

Adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA) version 23.0. AEs were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For each AE, start and stop date/times are collected as well as severity, a seriousness flag, treatment-relatedness, relatedness to procedures, action taken towards the study drug and outcome.

5.1.2 Derivation rules

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first administration of any study drug.

Based on their start date/time, AEs will be allocated to the phase and period during which they started. Each AE will therefore be reported in only one phase and period. Phases and periods are defined in section 2.2.1. In case the AE start date/time is incomplete or missing and the AE could consequently be allocated to more than one phase or period, a worst-case allocation will be done as detailed below:

- Treatment phase vs. screening phase: the AE will be allocated to the treatment phase unless the available parts of the AE start or stop date/time provide evidence for allocating to the screening phase.
- Multiple treatment periods: AE will be allocated to the first possible cycle + ITC period unless the available parts of the AE start or stop date/time provide evidence the assessments did not occur during that period.

A death case is defined as an AE with outcome ‘fatal’.

Adverse events of special interest will be defined using MedDRA SOC ‘Infections and infestations’.

Infusion-related reactions (IRR) will be defined as all AEs with a MedDRA preferred terms that are listed in either:

- MedDRA Hypersensitivity SMQ broad selection
- MedDRA Anaphylactic SMQ broad selection
- MedDRA Extravasation SMQ broad selection, excluding implants

AND occurring within 48 hours of an infusion, or within 2 days in case no AE start time is available.

An AE for which the study drug was discontinued is defined as an AE with action taken ‘drug withdrawn’.

Treatment-relatedness will be dichotomised as follows in tables:

- Treatment-related: related, probably related, possibly related or missing
- Not treatment-related: not related, unlikely related, not applicable

AE onset and duration will be calculated as follows when start and stop dates are fully known:

- AE onset day (vs. first administration)
  - AE start date ≥ date of first administration: AE start date – date of first administration + 1 day
  - AE start date < date of first administration: AE start date – date of first administration
- AE onset day (vs. start of period) = AE start date – cycle start date + 1 day
- AE duration (days) =
  - AE end date – AE start date + 1 day
  - study discontinuation date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study)

    In this case the duration will be presented as ">x days".

5.1.3 Presentation of results

Tables will present TEAEs only. AEs will be presented by cycle and overall. Pre-treatment AEs will only be listed.

An overview table will show the number and percentage of subjects with at least one event and the number of events for the following:

- TEAEs
- Serious TEAEs
- Grade ≥ 3 TEAEs
- TEAEs of special interest
- IRR events
- Fatal TEAEs
- Treatment-related TEAEs according to the Principle Investigator
- Procedures-related TEAEs
- Serious treatment-related TEAEs
- TEAEs for which the study drug was discontinued

This overview table will be repeated by showing the number of events per patient years of follow-up (per cycle and overall) to account for potential imbalance of follow-up time between the 2 treatment arms.

Summary tables by MedDRA system organ class and preferred term will show the number and percentage of subjects with at least one event. The table of TEAEs will additionally show the number of events. This table will be repeated by 3-monthly periods (90 days).

Separate tables will be prepared for the following TEAEs:

- Serious TEAEs
- Non-Serious TEAEs
- Grade ≥ 3 TEAEs
- TEAEs of special interest
- IRR events
- Treatment-related TEAEs
- Procedures-related TEAEs
- Serious treatment-related TEAEs
- Serious IRR events
- TEAEs for which the study drug was discontinued
- TEAE by ADA subject category per cycle
- TEAE by NAb subject category per cycle
- Adverse Events of Special Interest by MG therapies during the screening period*

*: MG therapies during the screening period will be classified as follows: NSID only, Steroid only, NSID+Steroid and none.

Additionally, a table showing time to first onset and duration of TEAEs of special interest will be prepared. For this table, only the overall period will be considered. For the duration, all AESI will be considered, not only the first in time.

All AEs, including pre-treatment events will be listed.

5.2 CLINICAL LABORATORY EVALUATION

5.2.1 Available data

Per protocol, the following laboratory parameters are expected:

- Biochemistry: Creatinine, creatinine clearance, blood urea nitrogen (BUN), glucose, glycosylated hemoglobin (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, albumin, potassium, sodium, calcium, lipid panel (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides), international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
- Haematology: Hemoglobin, platelet count, white blood cell (WBC) count with WBC differential
- Urinalysis: Color, clarity/appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination including red blood cell (RBC) count, WBC, cast crystals, bacteria.

- Serology: Human immunodeficiency virus (HIV) antibodies (1 and 2), Hepatitis B surface antigen (HBsAg), antibodies to the surface and core antigens of the hepatitis B virus (anti-HBs and anti-HBc), hepatitis C virus antibody (HCV-Ab)
- Other: Serum and urine human chorionic gonadotrophin (ß-HCG), Follicle-stimulating hormone (FSH) test

Normal ranges are available as provided by the laboratory.

5.2.2 Derivation rules

The following parameters will be derived:

- Estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)) (mL/min/1.73m²) = 141 * minimum(creatinine (mg/dL)/ K; 1)$^{\alpha}$ * maximum(creatinine (mg/dL)/ K; 1) $^{-1.209}$ * 0.993 $^{age\ (years)}$ * [1.018 if female] * [1.159 if race = black]

  where K = 0.7 if female and K = 0.9 if male;

  α = -0.329 if female and α = -0.411 if male

  Note: in case results in mg/dL are not available, results in µmol/L will be used after conversion in mg/dL: 1 µmol/L = 88.4 mg/dL
- Only fasted lipid samples and glucose (missing fasting status is considered as non-fasted) will be included in tabulations
- Lipid ratios (based on fasted samples only) will be rounded as detailed in section 2.3.3:
  - total cholesterol/HDL
  - LDL/HDL
  - HDL/LDL
- The following abnormality categories will be defined:
  - Low: value < lower limit of normal range
  - Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
  - High: value > upper limit of normal range

  Note:
  - Classification will be done in standardized units, using non imputed values and limits.
  - For the worst-case analysis visits, as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

Toxicity grades will be computed according to the National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) toxicity grading list (version 5.0). The implementation of these toxicity grades for analysis is presented in appendix 9.2. Only the parameters described in appendix 9.2 will be computed, according to the declared limits for each grade.

5.2.3 Presentation of results

Only continuous laboratory parameters expected per protocol will be tabulated and only for those analysis visits with at least 10 subjects (overall). The statistical analysis will present results in standardized units, except for corrected GFR, which will be reported in mL/min/1.73m2.

Continuous laboratory parameters will be summarized by means of descriptive statistics at each analysis visit. Categorical urinalysis and serology results will be listed only.

Laboratory abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline abnormality (SEB). Number of subjects with treatment-emergent abnormalities (see Definition of terms) will also be shown. The denominator for the percentage is the total number of subjects having data for the parameter per treatment and per analysis visit in the safety analysis set. Parameters for which toxicity grades are defined will not be included in the abnormalities tables.

Laboratory toxicity grades will be presented as cross-tabulations of the toxicity at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline toxicity. Numbers and cumulative numbers over decreasing toxicity grading of subjects with treatment-emergent toxicities will also be shown. The denominator for the percentage is the total number of subjects having data for the parameter per treatment and per analysis visit in the safety analysis set. Parameters having toxicity grades defined in both directions (hypo and hyper) will be shown by direction.

All laboratory data will be listed, but only for subjects with any post-baseline abnormality.

5.3 VITAL SIGNS

5.3.1 Available data

The following vital signs parameters are collected: systolic (SBP) and diastolic blood pressure (DBP) in supine position, pulse rate, body temperature and weight (only fixed on few visits, at other visits only in case of obvious weight change).

5.3.2 Derivation rules

Abnormalities are defined in below table.

	Pulse rate (bpm)	**SBP (mmHg)**	**DBP (mmHg)**	**Temperature (°C)**
Low	<40	<90	<45	<35.8
Normal	40-100	90-150	45-90	35.8-37.5
High	>100	>150	>90	>37.5

Note: For the worst-case analysis visits, as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

5.3.3 Presentation of results

Only analysis visits with at least 10 subjects (overall) will be tabulated. Vital signs parameters supine SBP, DBP and pulse rate will be summarized by means of descriptive statistics at each applicable analysis visit.

Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit versus the baseline abnormality (SEB) and as cross-tabulations of the worst-case abnormality versus the baseline abnormality (SEB). Number of subjects with treatment-emergent abnormalities will also be shown.

All vital signs data will be listed, but only for subjects with any post-baseline abnormality.

5.4 ELECTROCARDIOGRAMS

5.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected: heart rate (HR), RR interval, QRS interval, PR interval, QT interval, QTcF and QTcB.

5.4.2 Derivation rules

Abnormalities for HR, QRS and PR interval are defined in below table.

	HR (bpm)	PR (ms)	QRS (ms)
Low	<40	<120	-
Normal	40-100	120-220	0-120
High	>100	>220	>120

Note: For the worst-case analysis visit, as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

For QTcB and QTcF interval (ms), the following categories are defined:

- Actual values:
  - ≤ 450 (normal)
  -]450; 480]
  -]480; 500]
  - > 500
- Changes:
  - ≤ 30 (normal)
  -]30; 60]
  - > 60

Note: The worst-case, as defined in section 2.2.5, is the highest post-baseline value and associated change.

5.4.3 Presentation of results

Only analysis visits with at least 10 subjects (overall) will be tabulated. Uncorrected QT interval and RR will only be listed.

Continuous ECG parameters will be summarized by means of descriptive statistics at each analysis visit over time.

Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit, and at the worst-case analysis visit versus the baseline (SEB) abnormality. Numbers and cumulative numbers over decreasing abnormalities (QTc only) of subjects with treatment-emergent abnormalities will also be shown. The denominator for the percentage is the total number of subjects having data for the parameter per treatment and per analysis visit in the safety analysis set.

Abnormalities of the QTc changes will be presented as tabulations of the change abnormality at each post-baseline analysis visit and at the worst-case analysis visit. Cumulative numbers over decreasing change abnormalities of subjects will also be shown. The denominator for the percentage is the total number of subjects having data for the parameter per treatment and per analysis visit in the safety analysis set.

All ECG data will be listed, but only for subjects with any post-baseline abnormality.

5.5 SUICIDALITY ASSESSMENT

5.5.1 Available data

This so-called suicidality assessment will be conducted by specifically asking the following question, derived from the PHQ-9: "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?" Possible outcomes: Not at all (0), Several days (1), More than half the days (2), Nearly every day (3)

5.5.2 Presentation of results

Suicidality assessment results will be presented using a frequency tabulation by analysis visit and worst-case over time. The denominator for the percentage is the total number of subjects per treatment and per analysis visit in the safety analysis set.

All suicidality assessment data will be listed, but only for subjects with any post-baseline category ≥ 1.

6. CHANGES TO THE PLANNED ANALYSIS

6.1 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS BEFORE DATABASE LOCK

PK parameter AUC_{0-t} will be calculated for the Japanese subjects on Visit 1 and 4.

6.2 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS AFTER DATABASE LOCK

NA

6.3 CHANGES TO THE FINAL STATISTICAL ANALYSIS PLAN

The following updates were done on sponsor's request, after testruns and prior to database lock:

Section	Section title	Change description
2.1.2	As planned vs. as actual analysis	In case of misdosing during one infusion, actual treatment would remain equal to planned treatment.
2.2.1	Phases and periods	End phase with date of trial termination iso date of last contact
2.3.2	Values below or above a threshold	Disregarding PD results above ULOQ from analysis
2.4	Presentation of results	Adding a statement for the J-MAA submission analysis
2.4.1	Presentation of results	Tables by analysis visits are limited to analysis visits with at least 10 subjects.
3.1	Subject disposition	Adding a listing with COVID-19 related comments
3.5.3	Prior and concomitant therapies - presentation of results	Adding number of patients with at least 1/2/3 MG therapies to the MG therapy tables.
4.1.3	Efficacy - presentation of results	Adding tables with logistic regression results for MG-ADL and QMG response in cycle 2
		Adding tables with descriptive statistics of MG-ADL by number of cycles
4.3.2	Pharmacodynamics - derivation rules	Adding analysis timepoint 'minimum value/ maximal drop' to the pharmacodynamics tables
5.1.2	Adverse events - derivation rules	Adding definition of infusion-related reactions (IRR)
5.1.3	Adverse events - presentation of results	Adding tables on IRR
5.2.2	Clinical laboratory evaluation - derivation rules	Replacing eGFR formula: formula for creatinine in mg/dL iso µmol/L
		Disregarding non-fasted glucose samples in analysis
5.3.3	Vital signs - presentation of results	Removing weight and body temperature from tables

Additionally, some minor updates were done to correct typo's or to add clarifications, with no impact on the analysis.

7. REFERENCES

ICH E3: Structure and Content of Clinical Study Reports, July 1996

ICH E6: Guideline for Good Clinical Practice, December 2016

ICH E9: Statistical Principles for Clinical Trials, September 1998

ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) – questions and answers, January 2016.

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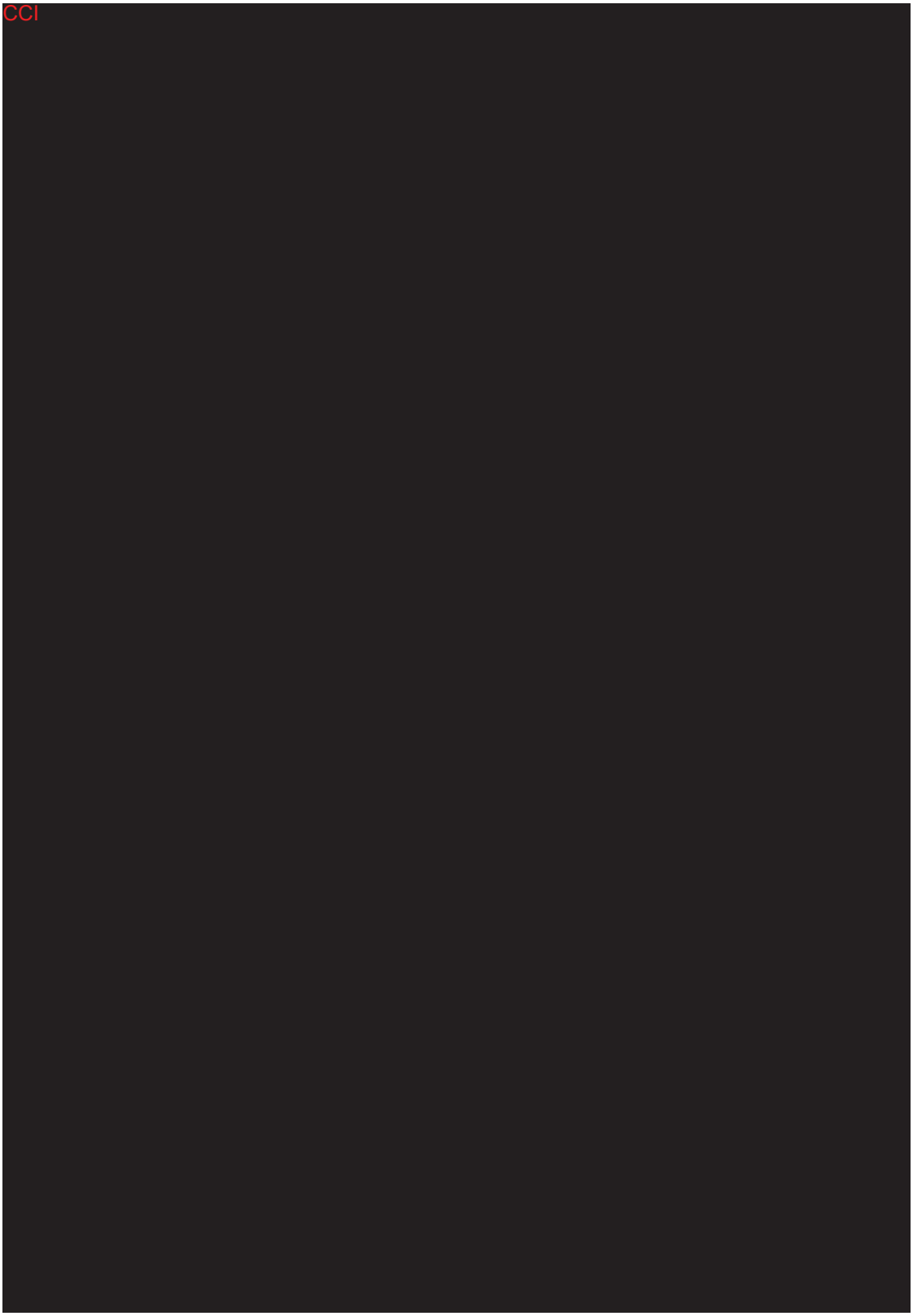

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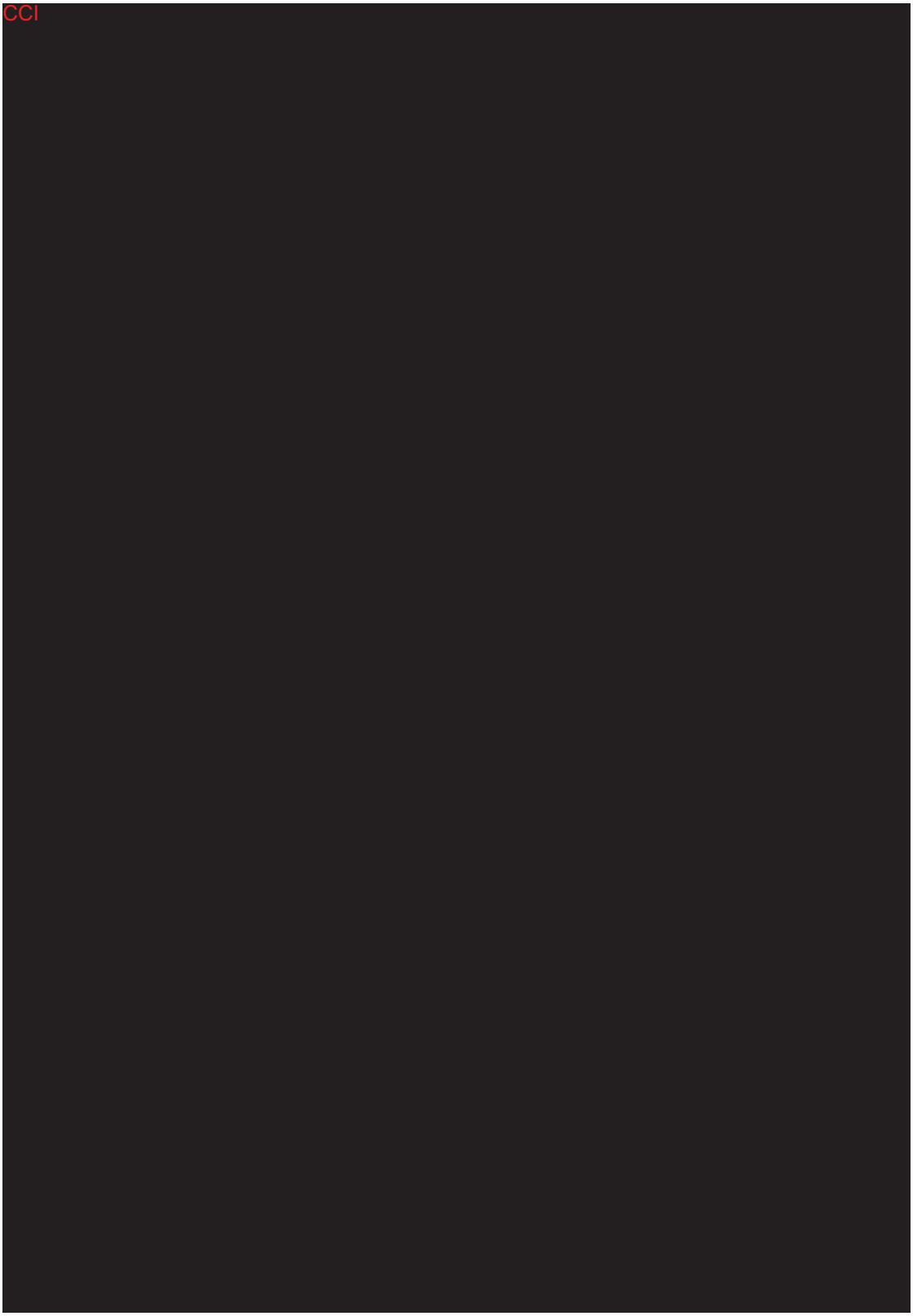

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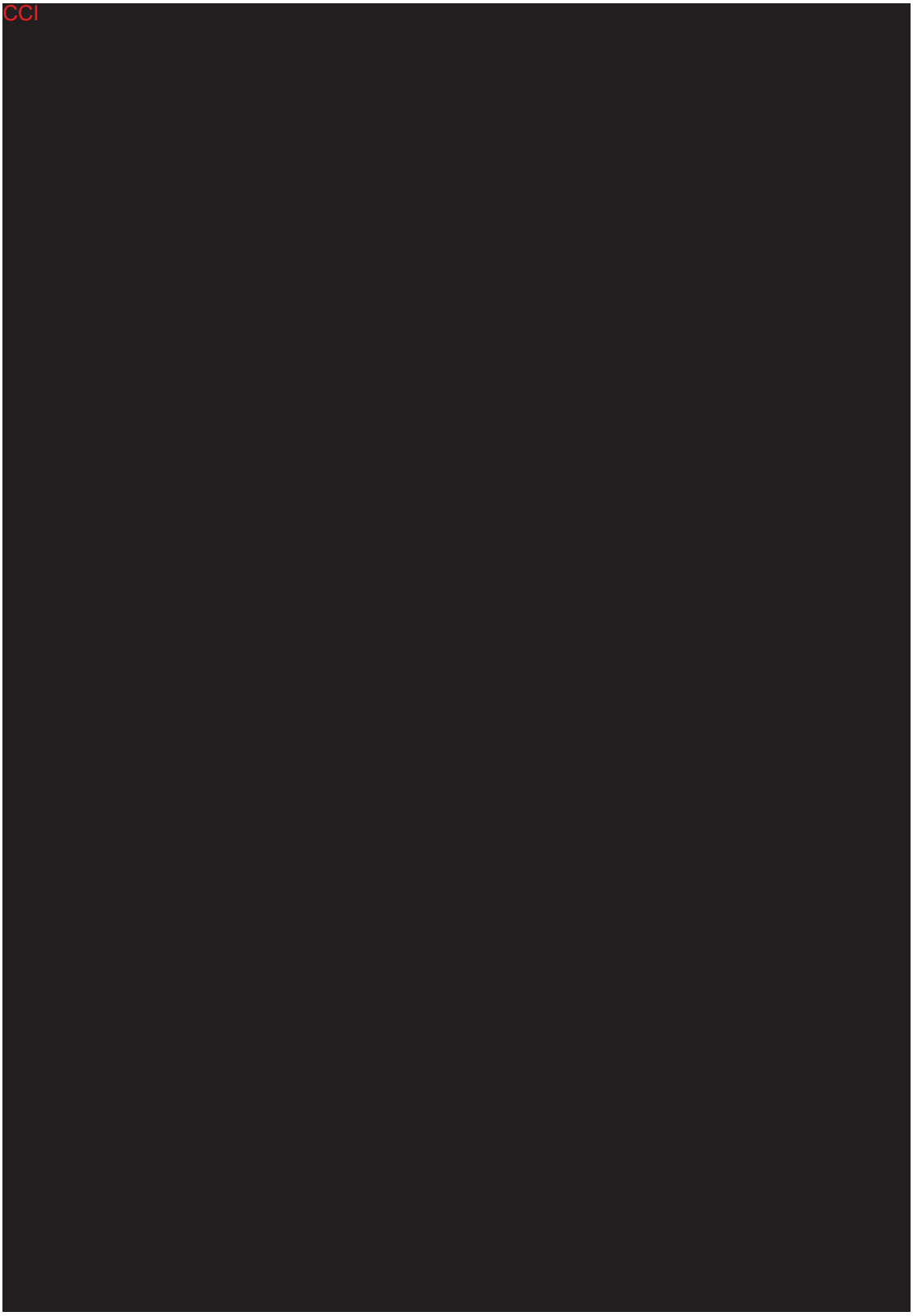

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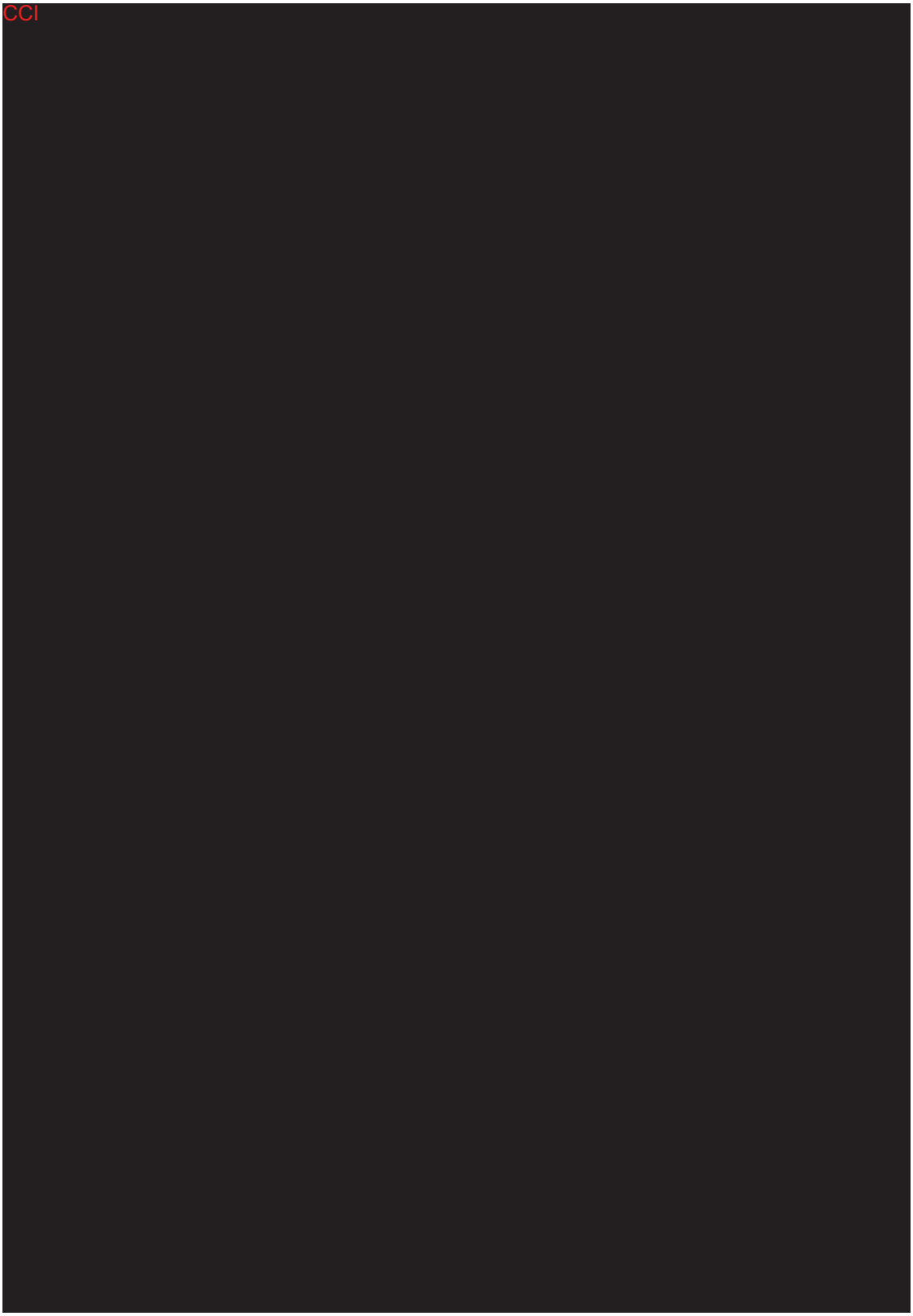

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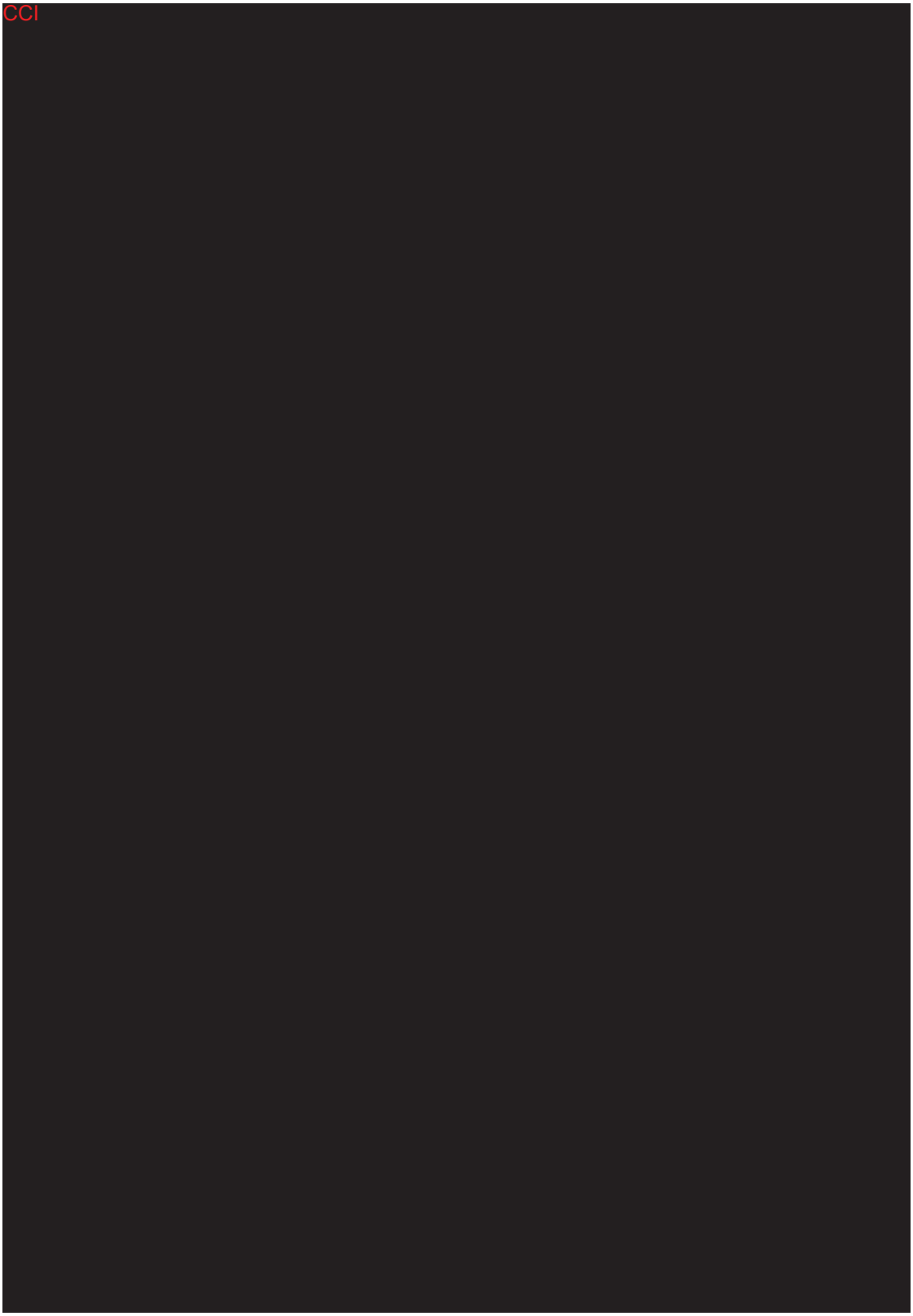

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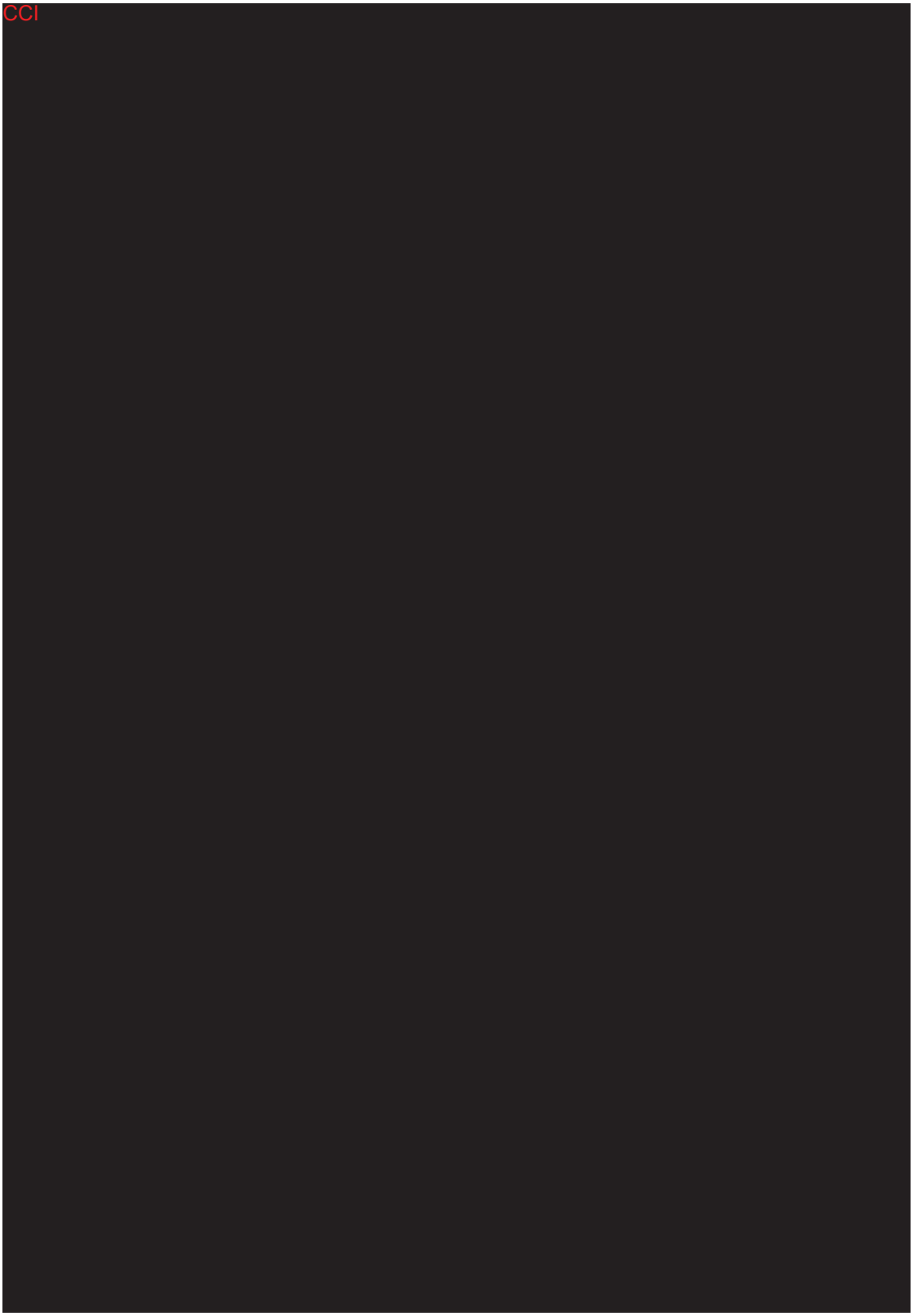

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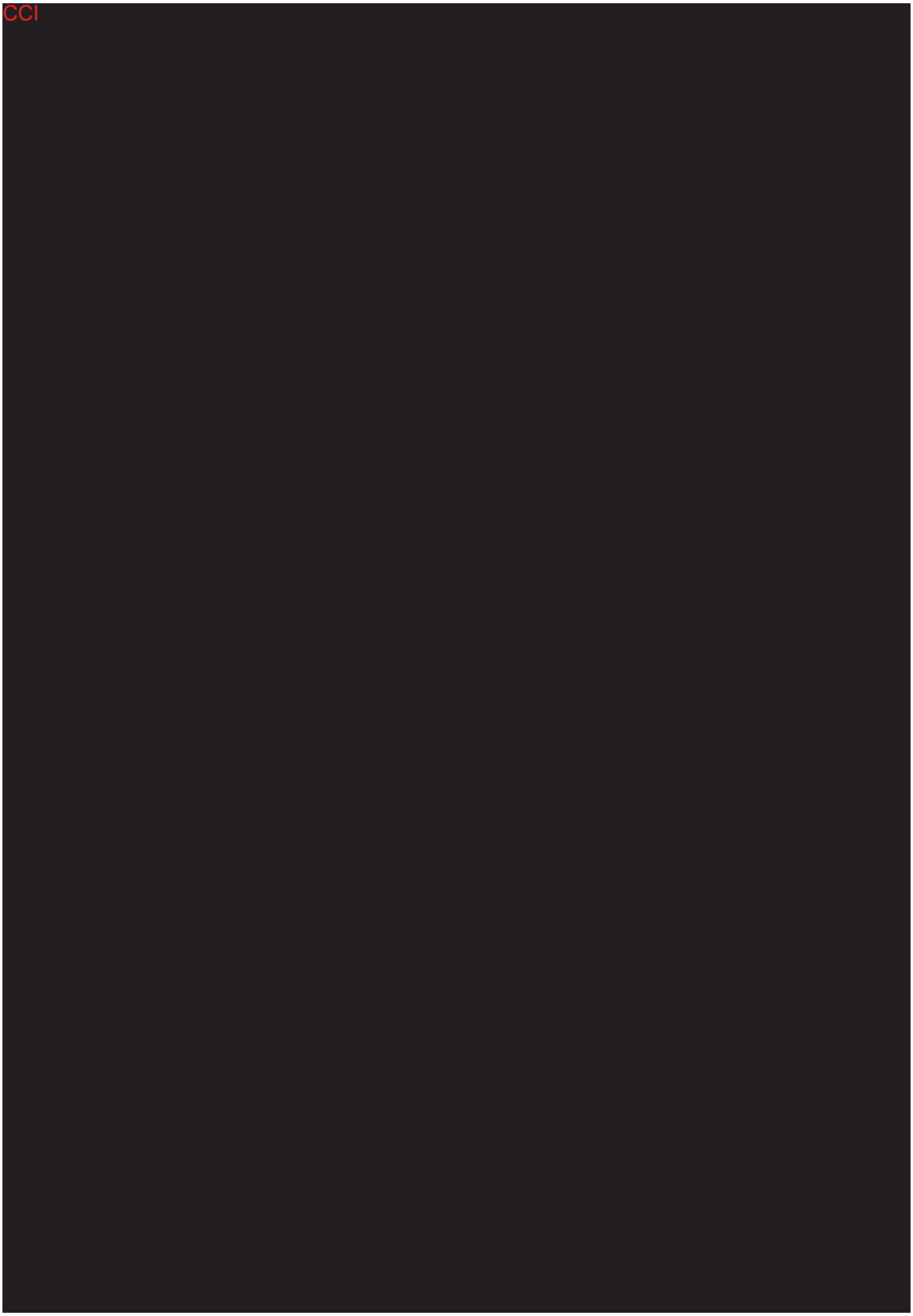

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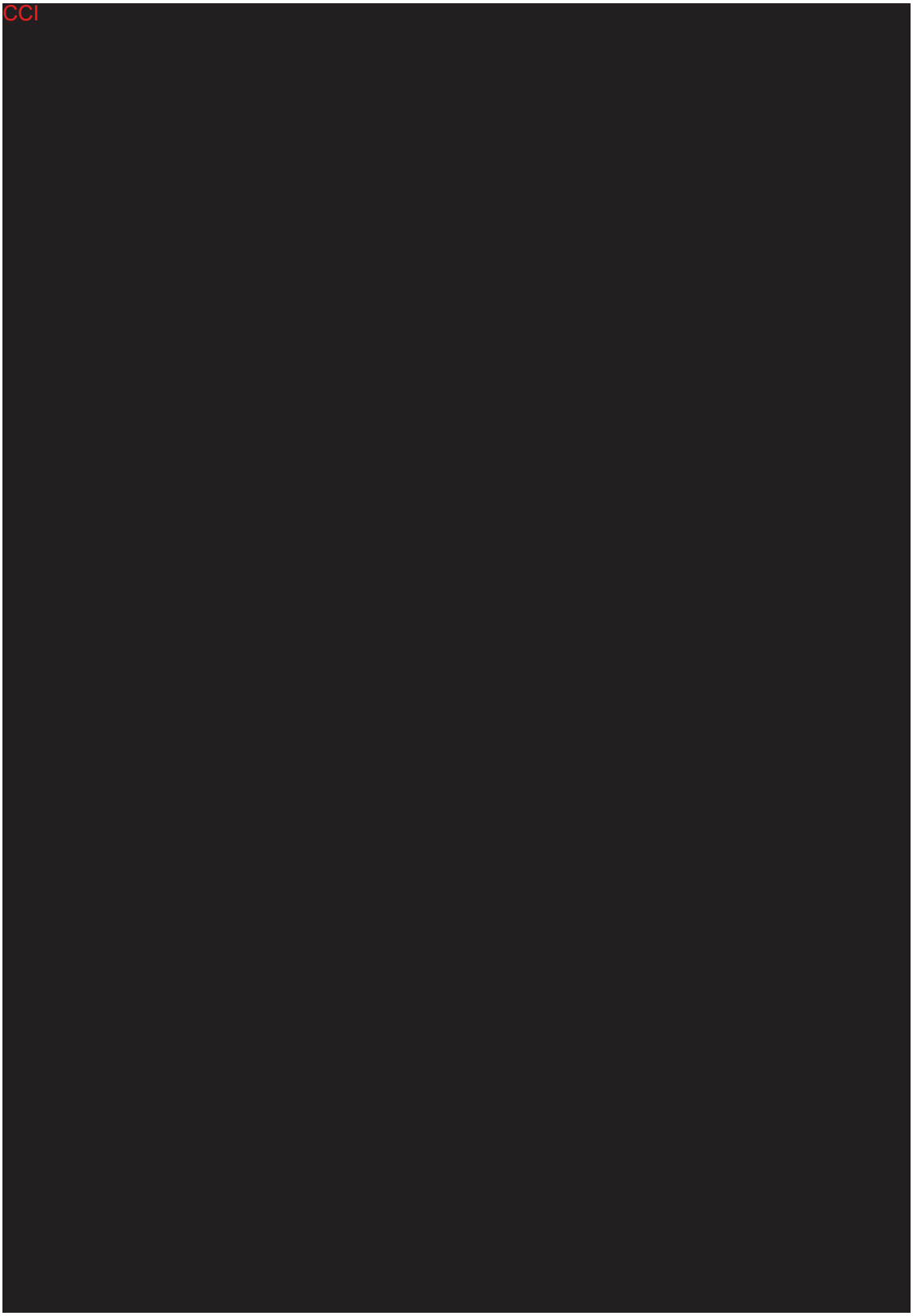

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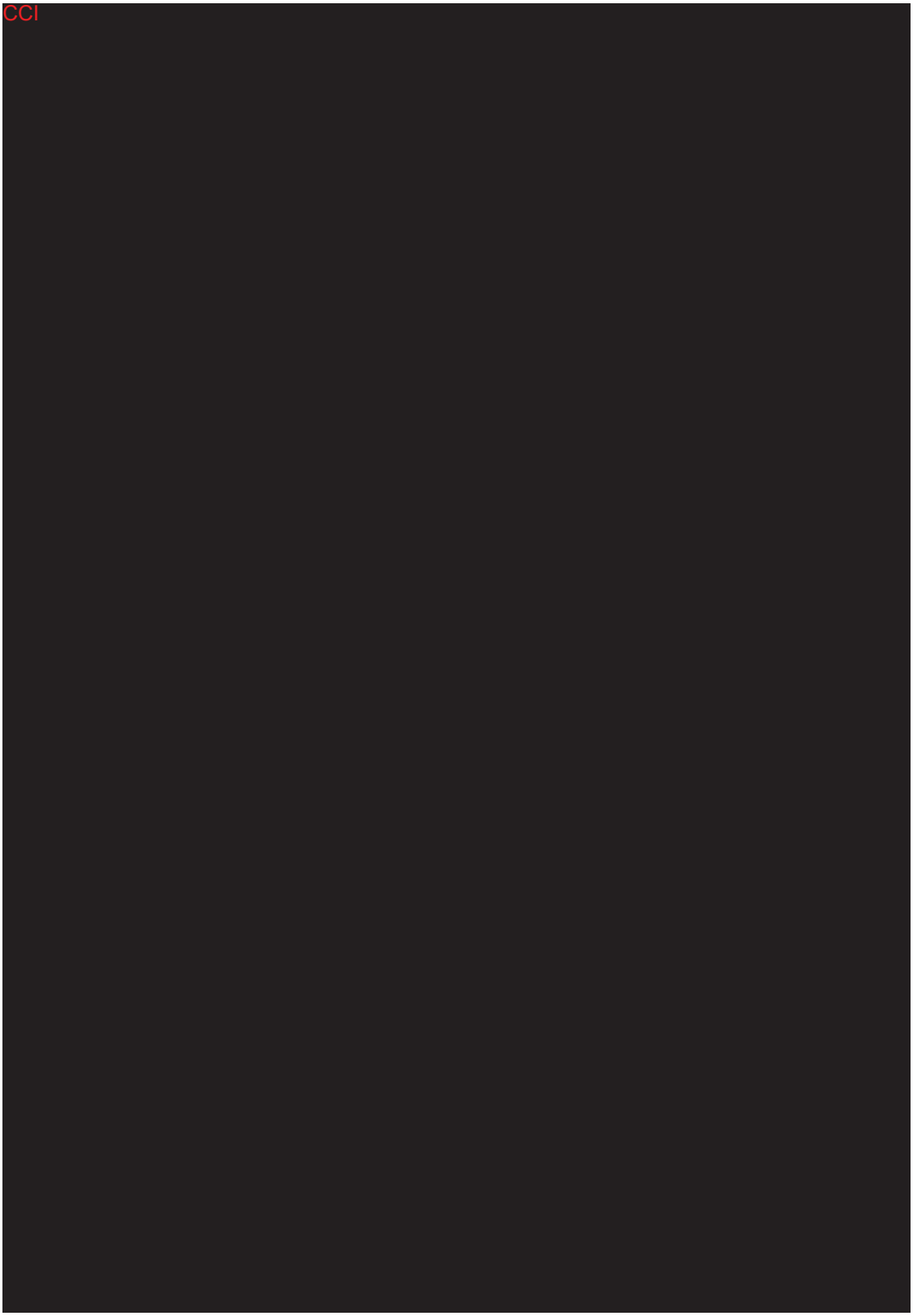

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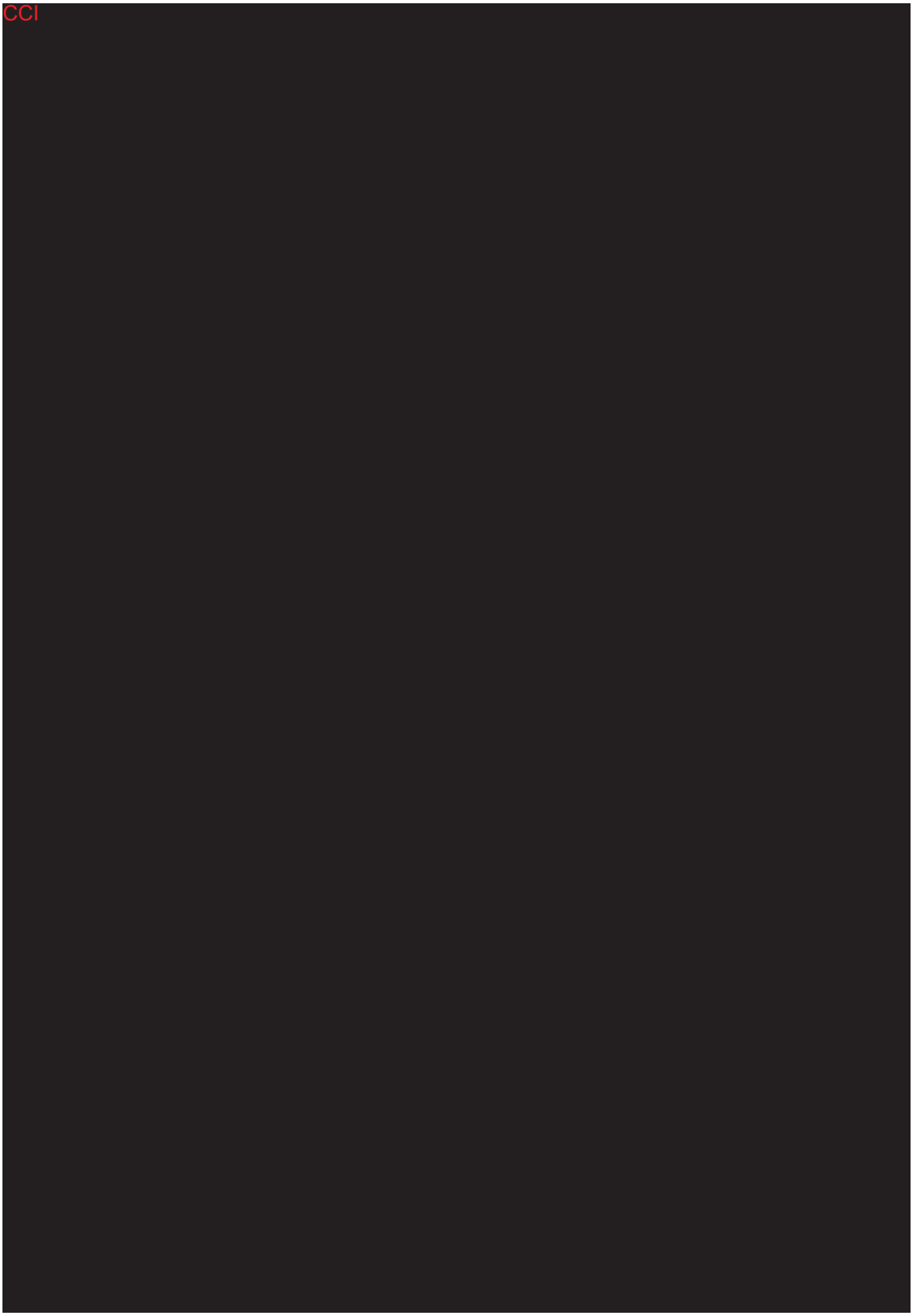

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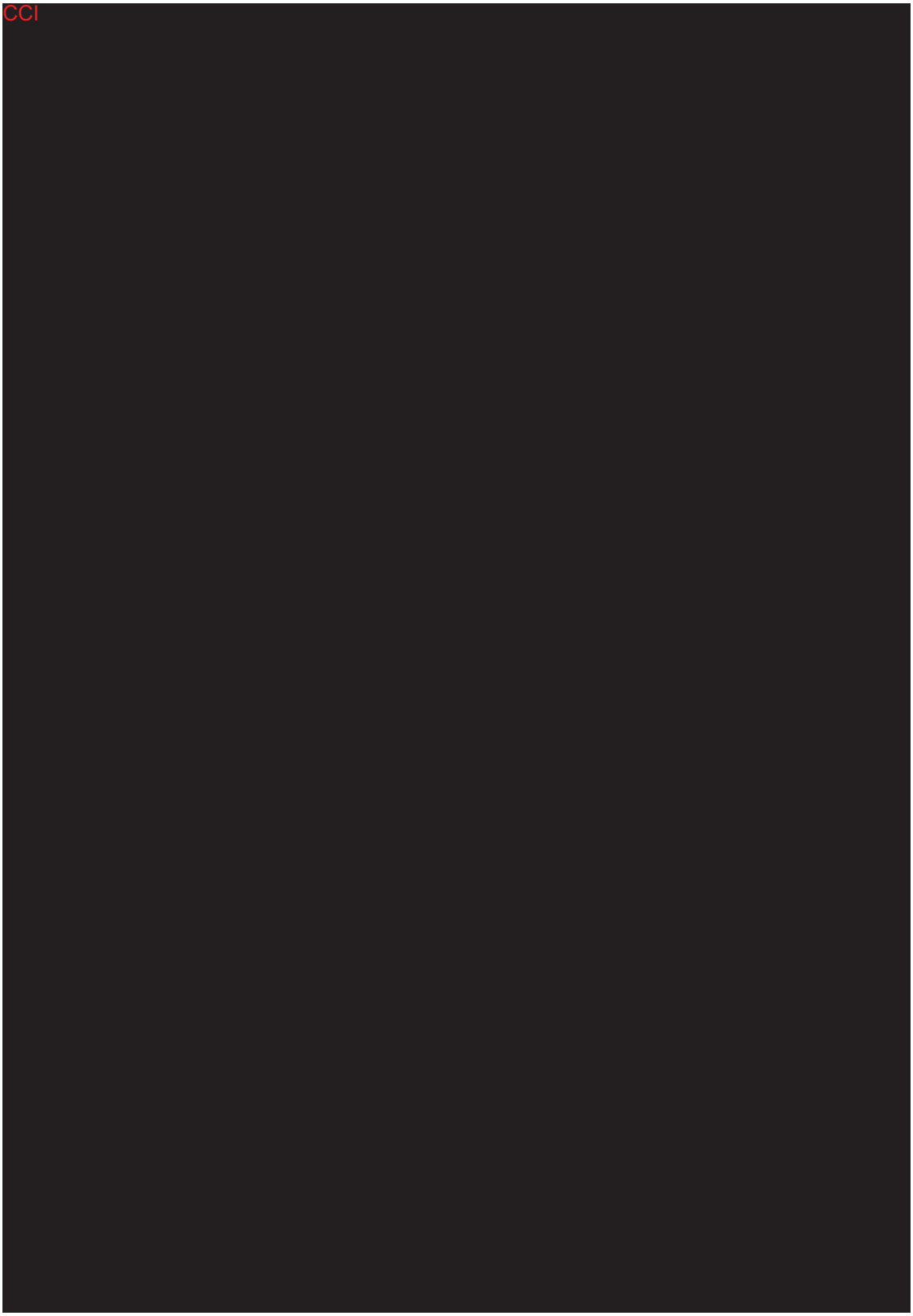

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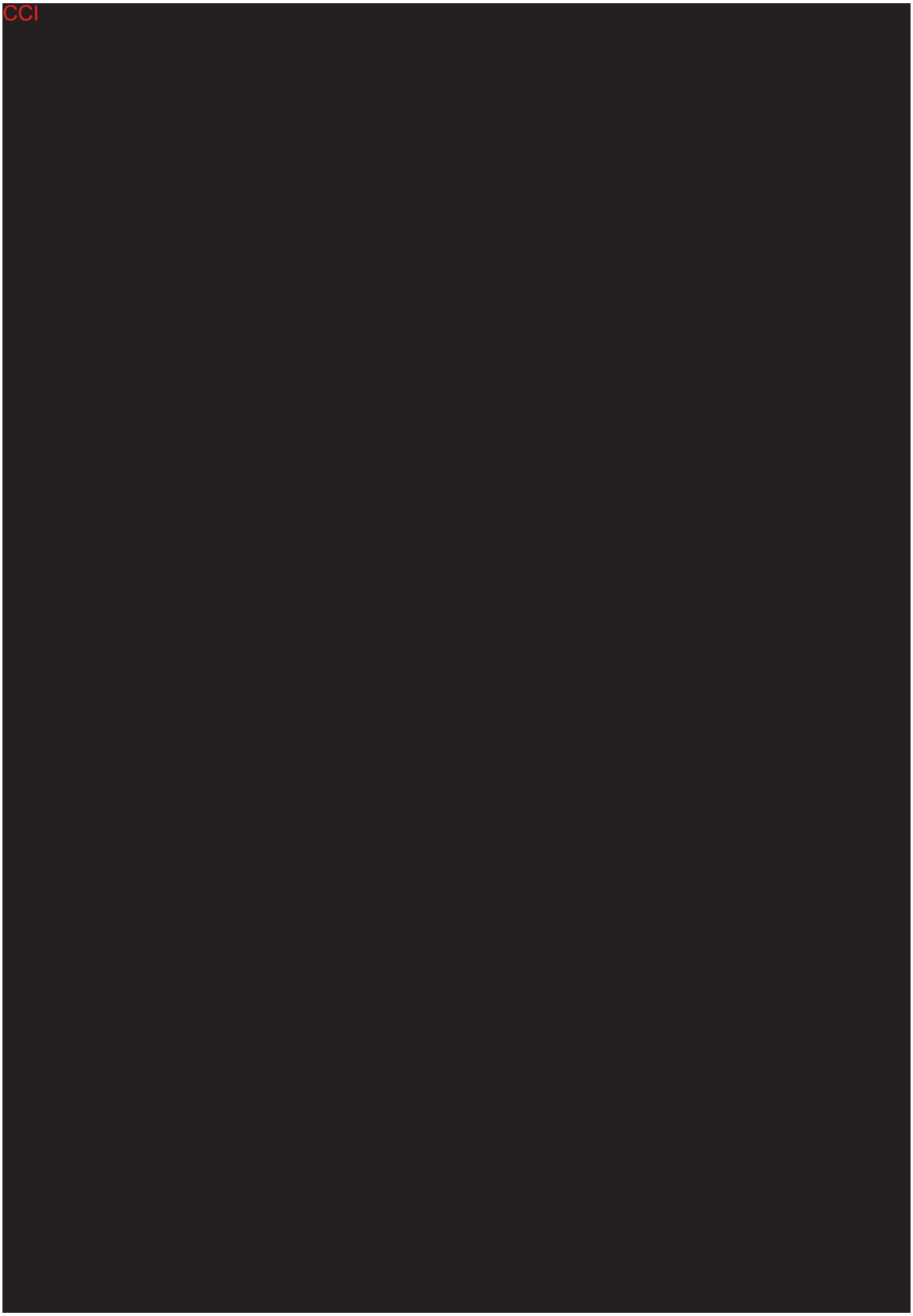

9. APPENDICES

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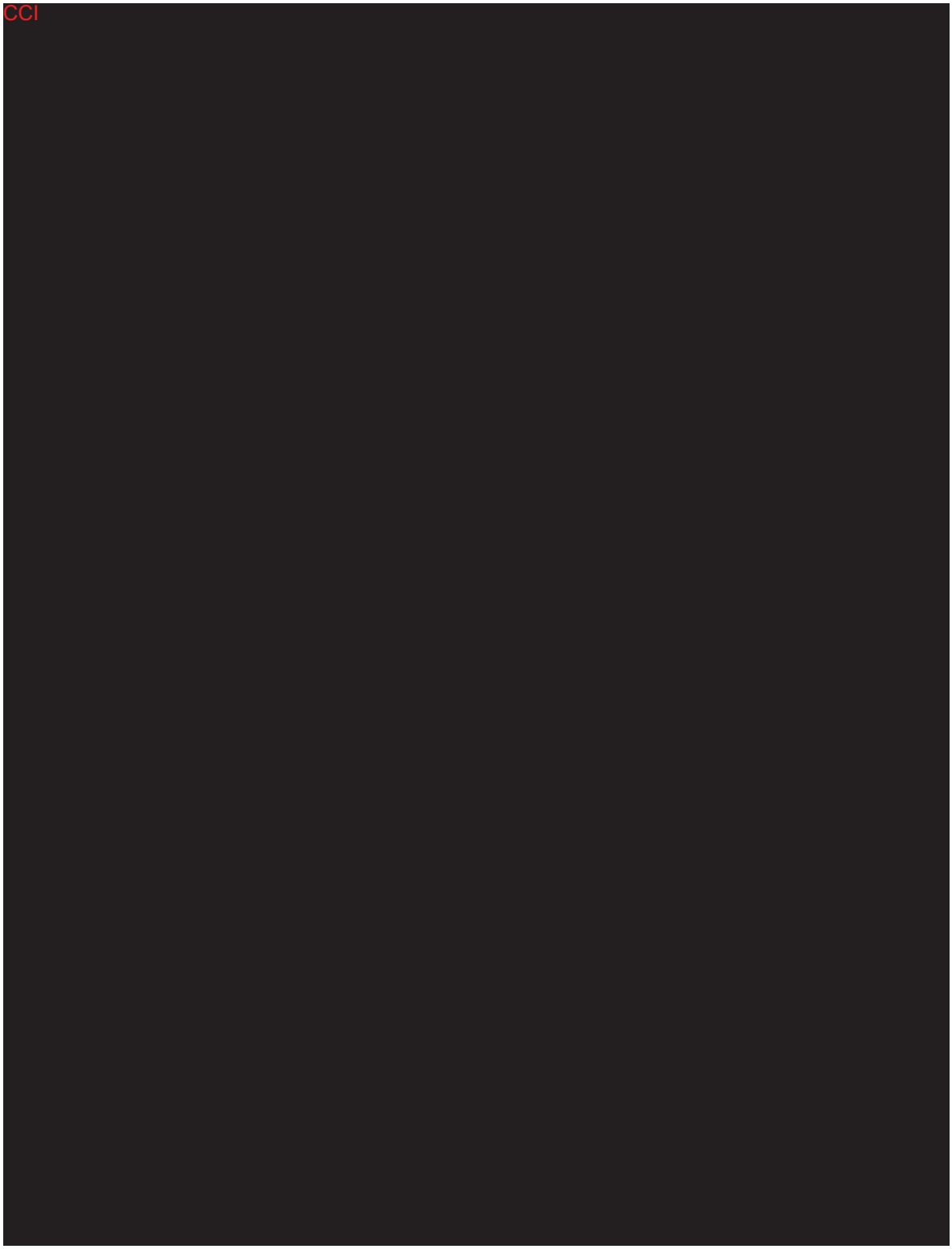

SGS	Statistical Analysis Plan	
ARGX-113-1704	Final analysis	Final 2.0. of 08MAY2020

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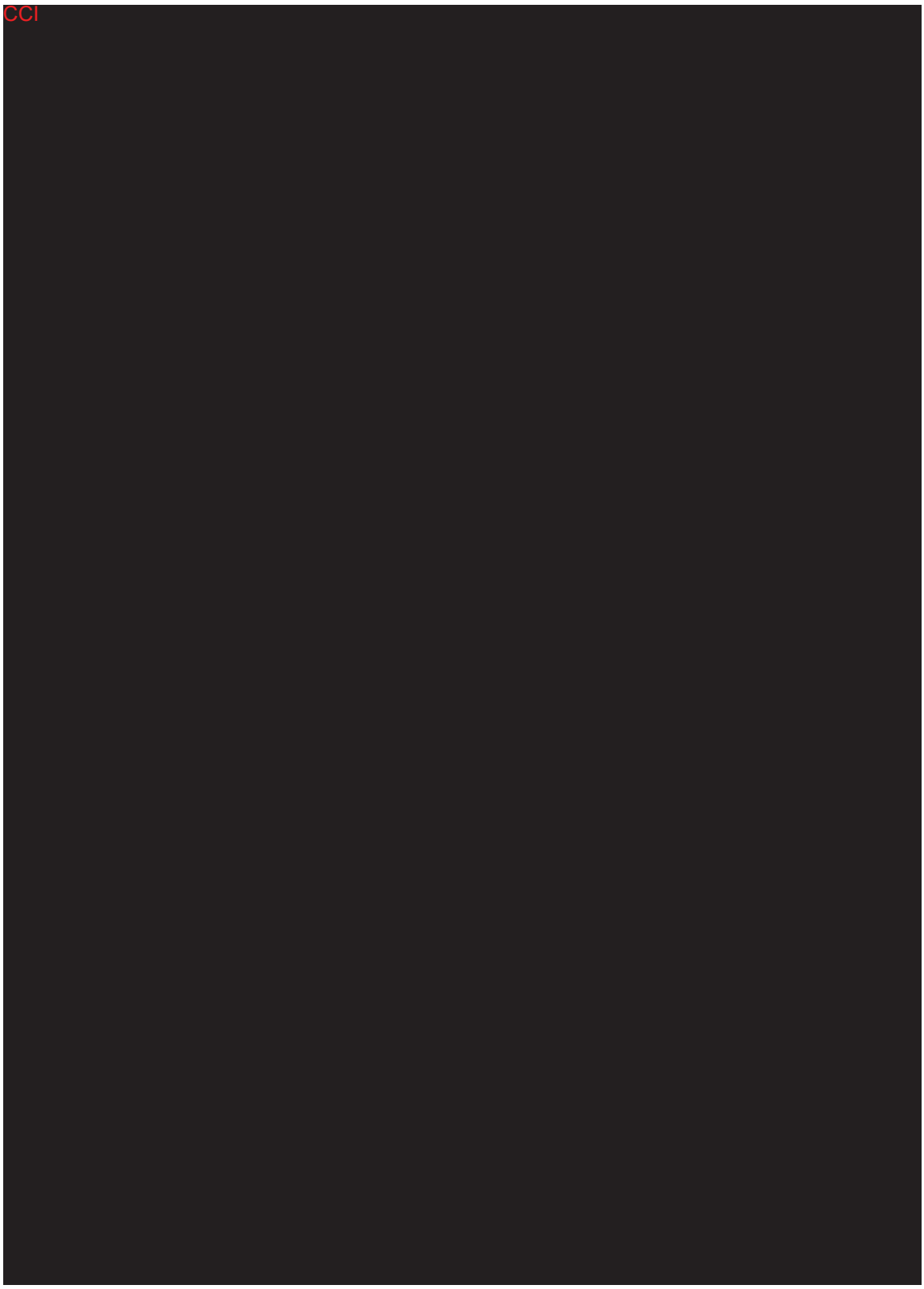
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9.2 TOXICITY GRADES

Common Terminology Criteria for Adverse Events CTCAE, v5.0: November 27, 2017

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Amylase (pancreatic)		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Alanine amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Albumin	g/L	<LLN-30	<30-20	<20	-
	g/dL	<LLN-3	<3-2	<2	-
Alkaline phosphatase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Aspartate amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Bilirubin (total)		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-10.0 *ULN	>10.0 *ULN
Calcium (ionized) low	mmol/L	<LLN-1.0	<1.0-0.9	<0.9-0.8	<0.8
	mg/dL	<LLN-4.0	<4.0-3.6	<3.6-3.2	<3.2
Calcium (ionized) high	mmol/L	>ULN-1.5	>1.5-1.6	>1.6-1.8	>1.8
	mg/dL	>ULN-6.0	>6.0-6.4	>6.4-7.2	>7.2
Calcium (corrected) low	mmol/L	<LLN-2.00	<2.00-1.75	<1.75-1.50	<1.50
	mg/dL	<LLN-8	<8-7	<7-6	<6
Calcium (corrected) high	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
	mg/dL	>ULN-11.5	>11.5-12.5	>12.5-13.5	>13.5
Cholesterol	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
	mg/dL	>ULN-300	>300-400	>400-500	>500

Creatine kinase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN
Creatinine		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-6.0 *ULN	>6.0 *ULN
Gamma-glutamyl transferase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Glucose (fasting) low	mmol/L	<LLN-3.0	<3.0-2.2	<2.2-1.7	<1.7
	mg/dL	<LLN-55	<55-40	<40-30	<30
Lipase		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Magnesium low	mmol/L	<LLN-0.5	<0.5-0.4	<0.4-0.3	<0.3
	mg/dL	<LLN-1.2	<1.2-0.9	<0.9-0.7	<0.7
Magnesium high	mmol/L	>ULN-1.23	-	>1.23-3.30	>3.30
	mg/dL	>ULN-3.0	-	>3.0-8.0	>8.0
Potassium low	mmol/L	-	<LLN-3.0	<3.0-2.5	<2.5
	mEq/L	-	<LLN-3.0	<3.0-2.5	<2.5
Potassium high	mmol/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
	mEq/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Sodium low	mmol/L	<LLN-130	-	<130-120	<120
	mEq/L	<LLN-130	-	<130-120	<120
Sodium high	mmol/L	>ULN-150	>150-155	>155-160	>160
	mEq/L	>ULN-150	>150-155	>155-160	>160
Triglycerides	mmol/L	1.71-3.42	>3.42-5.70	>5.70-11.4	>11.4
	mg/dL	150-300	>300-500	>500-1000	>1000

Partial thromboplastin time (activated or not specified		>1.0-1.5 *ULN	>1.5-2.5 *ULN	>2.5 *ULN	-
CD4 count	giga/L	<LLN-0.50	<0.50-0.20	<0.20-0.05	<0.05
	counts/mm3	<LLN-500	<500-200	<200-50	<50
Fibrinogen		<1.00-0.75 *LLN	<0.75-0.50 *LLN	<0.50-0.25 *LLN	<0.25 *LLN
International normalized ratio		>1.2-1.5 *ULN	>1.5-2.5 *ULN	>2.5 *ULN	-
Lymphocytes (absolute count) low	giga/L	<LLN-0.80	<0.80-0.50	<0.50-0.20	<0.20
	counts/mm^3	<LLN-800	<800-500	<500-200	<200
Lymphocytes (absolute count) high	giga/L	-	>4-20	>20	-
	counts/mm^3	-	>4000-20000	>20000	-
Neutrophils (absolute count) low	giga/L	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
	counts/mm^3	<LLN-1500	<1500-1000	<1000-500	<500
Platelets	giga/L	<LLN-75	<75-50	<50-25	<25
	counts/mm^3	<LLN-75000	<75000-50000	<50000-25000	<25000
White blood cells	giga/L	<LLN-3	<3-2	<2-1	<1
	counts/mm^3	<LLN-3000	<3000-2000	<2000-1000	<1000

Note: In case ULN/LLN is higher/lower than the upper/lower limit of grade 1 (or even higher grades), ULN/LLN will be ignored and only the fixed values of CTCAE will be considered.

9.3 MG THERAPIES AND PROCEDURES

Steroids	NSID's	AChE inhibitors	Procedures
PREDNISONE	CICLOSPORIN	NEOSTIGMINE	PLASMAPHERESIS
PREDNISOLONE	AZATHIOPRINE	NEOSTIGMINE BROMIDE	IMMUNOGLOBULIN THERAPY
METHYLPREDNISOLONE	MYCOPHENOLATE MOFETIL	PYRIDOSTIGMINE	THYMECTOMY
HYDROCORTISONE	MYCOPHENOLATE SODIUM	PYRIDOSTIGMINE BROMIDE	
TRIAMCINOLONE	MYCOPHENOLIC ACID	AMBENONIUM	
	METHOTREXATE	AMBENONIUM CHLORIDE	
	TACROLIMUS	DISTIGMINE	
	CYCLOPHOSPHAMIDE	DISTIGMINE BROMIDE	
	CYTOPHOSPHANE		

9.4 SCHEDULE OF ASSESSMENTS

9.4.1 Main Study

General Schedule of Assessments

Assessment	Screening	Treatment Period				Follow-up (FU) Period					ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1V2	TC_1V3	TC_1V4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9	ITC_nVn	EoS/ED	UNS[u]
Trial Day (Visit Window)	Day -14 to -1	1	8±1	15±1	22±1	29±1	36±1	43±1	50±1	57±1			
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_nB)	TC_nV2	TC_nV3	TC_nV4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+7)±1	(X+14)±1	(X+21)±1	(X+28)±1	(X+35)±1	(X+42)±1	(X+49)±1	(X+56)±1	Y±2	182±3	
					EoT[v]								
Informed consent[c]	X												
Inclusion/exclusion criteria	X	X											
Medical/surgical history	X												
Demographic characteristics	X												
Randomization[d]		X											
MG-ADL[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
QMG[e]		X	X	X	X	X	X	X	X	X	X	X	X

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

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

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

[e] The Inter Treatment Cycle (ITC) period consists of visits every 2 weeks, starting 14 days (± 2 days) from the last visit of the previous Treatment Cycle. The visit denominator ('n') will start at 1 at each period. At each ITCnV, an evaluation of the need for re-treatment should be done prior to decide whether assessments listed for ITCnV or TCnV1 are to be performed.

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

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

[h] Randomization (at the first Treatment Cycle Baseline [TC1B] only) should be performed as soon as possible after Screening with a maximum of 2 weeks, however only after confirmation of eligibility of the patient.

[i] Efficacy and quality of life assessments should be completed pre-dose on each dosing day and should be performed prior to any other trial-specific assessment, except for obtaining informed consent at Screening and the weight assessment, if applicable. The MG-ADL scale needs to be performed prior to all other efficacy or quality of life assessments. Acetylcholinesterase (AChE) inhibitors must be halted for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]). A total MG-ADL score ≥ 5 with more than 50% of this total score attributed to non-ocular symptoms should be met at Screening and Baseline (CnB).

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

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

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

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

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

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

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

[q] A serum pregnancy test will be performed on the samples taken for clinical laboratory tests (only for women of childbearing potential).

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

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

[t] Viral tests will be performed on samples taken at Screening (see protocol appendix 6).

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

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

[w] The Investigational Medicinal Product (IMP; ARGX-113 or placebo) will be administered as an intravenous (IV) infusion over a period of 1 hour at Visits 1, 2, 3, and 4. Patients will remain at the site for at least 1 hour following the end of the infusion for safety monitoring based on the patient's clinical status.

[x] At TCnV1, the conditions for re-treatment will be checked before administration of the IMP.

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

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

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

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

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

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

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

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

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

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

[e] Disease severity assessments should be performed prior to any other trial-specific assessment in the following sequence: 1) MG-ADL, 2) QMG. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]).

[f] A urine pregnancy test will be performed only for women of childbearing potential.

9.4.2 Japan amendment

General Schedule of Assessments

Assessment	Screening	Treatment Period						Follow-up (FU) Period							ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1 PK1	TC_1 PK2	TC_1V2	TC_1V3	TC_1V4	TC_1 PK3	TC_1 PK4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9	ITC_nVn	EoS/ED	UNS[u]
Trial Day (Visit Window)	Day -14 to -1	1	3±1	5±1	8±1	15±1	22±1	24 ±1	26 ±1	29±1	36±1	43±1	50±1	57±1[y]			
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_nB)	TC_n PK1	TC_n PK2	TC_nV2	TC_nV3	TC_nV4	TC_n PK3	TC_n PK4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+2) ±1	(X+4) ±1	(X+7) ±1	(X+14) ±1	(X+21) ±1	(X+23) ±1	(X+25) ±1	(X+28) ±1	(X+35) ±1	(X+42) ±1	(X+49) ±1	(X+56) ±1[y]	Y±2	182±3[x]	
							EoT[v]										
Informed consent[c]	x																
Inclusion/exclusion criteria	x	x															
Medical/surgical history	x																
Demographic characteristics	x																
Randomization[d]		x															
MG-ADL[e]	x	x			x	x	x			x	x	x	x	x	x	x	x
QMG[e]		x			x	x	x			x	x	x	x	x	x	x	x
MGC[e]		x			x	x	x			x	x	x	x	x	x	x	x
EQ-5D-5L[e]		x			x	x	x			x	x	x	x	x	x	x	x

Assessment	Screening	Treatment Period						Follow-up (FU) Period							ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1 PK1	TC_1 PK2	TC_1V2	TC_1V3	TC_1V4	TC_1 PK3	TC_1 PK4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9	ITC_nVn	EoS/ED	UNS[u]
Trial Day (Visit Window)	Day -14 to -1	1	3±1	5±1	8±1	15±1	22±1	24 ±1	26 ±1	29±1	36±1	43±1	50±1	57±1[y]			
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_nB)	TC_n PK1	TC_n PK2	TC_nV2	TC_nV3	TC_nV4	TC_n PK3	TC_n PK4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+2) ±1	(X+4) ±1	(X+7) ±1	(X+14) ±1	(X+21) ±1	(X+23) ±1	(X+25) ±1	(X+28) ±1	(X+35) ±1	(X+42) ±1	(X+49) ±1	(X+56) ±1[y]	Y±2	182±3[x]	
							EoT[v]										
MG-QoL15r[e]		x			x	x	x			x	x	x	x	x	x	x	x
Suicidality assessment[f]	x	x			x	x	x			x	x	x	x	x	x	x	x
Physical examination[g]	x	x			x	x	x			x	x	x	x	x	x	x	x
Height and weight[h]	x															x	
Vital signs[i]	x	x			x	x	x			x	x	x	x	x	x	x	x
ECG[j]	x	x			x	x	x			x	x	x	x	x	x	x	x
Clinical laboratory tests[k]	x	x			x	x	x			x	x	x	x	x	x	x	x
AChR-/MuSK-antibody serotype	x																
Urinalysis[l]	x	x			x	x	x			x	x	x	x	x	x	x	x
Serum pregnancy test[m]	x																

Assessment	Screening	Treatment Period						Follow-up (FU) Period							ITC Period[a]	End of Study / Early Discontinuation	Unscheduled
Visits Treatment Cycle 1	SCR	TC_1V1 (SEB)	TC_1 PK1	TC_1 PK2	TC_1V2	TC_1V3	TC_1V4	TC_1 PK3	TC_1 PK4	TC_1V5	TC_1V6	TC_1V7	TC_1V8	TC_1V9	ITC_nVn	EoS/ED	UNS[u]
Trial Day (Visit Window)	Day -14 to -1	1	3±1	5±1	8±1	15±1	22±1	24 ±1	26 ±1	29±1	36±1	43±1	50±1	57±1[y]			
Visits Subsequent Treatment Cycle(s)[b]		TC_nV1 (TC_n B)	TC_n PK1	TC_n PK2	TC_n V2	TC_n V3	TC_n V4	TC_n PK3	TC_n PK4	TC_nV5	TC_nV6	TC_nV7	TC_nV8	TC_nV9			
Trial Day (Visit Window)		X	(X+2) ±1	(X+4) ±1	(X+7) ±1	(X+14) ±1	(X+21) ±1	(X+23) ±1	(X+25) ±1	(X+28) ±1	(X+35) ±1	(X+42) ±1	(X+49) ±1	(X+56) ±1[y]	Y±2	182±3[x]	
							EoT[v]										
Urine pregnancy test[n]		x			x	x	x			x	x	x	x	x	x	x	x
Anti-AChR/anti-MuSK antibodies[o]		x			x	x	x			x	x	x	x	x	x	x	x
Total IgG and its subtypes[o]		x			x	x	x			x	x	x	x	x	x	x	x
Viral tests[p]	x																
ADA[q]		x					x[q]				x[q]			x		x	x
Pharmacokinetics[r]		x	x[r]	x[r]	x	x	x	x[r]	x[r]	x	x					x	x
Administration of ARGX-113 or placebo[s]		x[t]			x	x	x										
Prior[w]/concomitant/ rescue therapy	<---------- x ---------->																
Adverse events	<---------- x ---------->																

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

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

[b] Last Treatment Cycle in the trial should not start later than on Day 127 of the trial or 7th February 2020, whichever comes first. If the patient is in need of re-treatment after this date, the patient should have the EoS/ED visit performed and, if eligible, he/she can roll-over into the long-term, single-arm, open-label follow-on ARGX-113-1705 trial.

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

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

[e] Efficacy and quality of life assessments should be completed pre-dose on each dosing day and should be performed prior to any other trial-specific assessment, except for obtaining informed consent at Screening and the weight assessment, if applicable. The MG-ADL scale needs to be performed prior to all other efficacy or quality of life assessments. Acetylcholinesterase (AChE) inhibitors must be halted for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]). A total MG-ADL score ≥ 5 with more than 50% of this total score attributed to non-ocular symptoms should be met at Screening and Baseline (TC_nB).

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

[g] The physical examination will be performed pre-dose on dosing days. See Section 7.2 3 of the protocol for an overview of the different assessments.

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

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

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

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

[l] Urine samples will be collected pre-dose on dosing days (see appendix 6 of the protocol).

[m] A serum pregnancy test will be performed on the samples taken for clinical laboratory tests (only for women of childbearing potential, see definition of terms of the protocol)

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

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

[p] Viral tests will be performed on samples taken at Screening (see appendix 6 of the protocol).

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

[r] Pharmacokinetic (PK) samples will be collected at Visits 1, 2, 3, 4, 5, 6 and PK1, PK2, PK3 and PK4 in each Treatment Cycle, at EoS/ED, and at UNS. On dosing days, PK samples will be collected pre dose (within 1 hour prior to start of infusion) and after the end of each infusion (within 1 hour after end of infusion). Visits PK1 and PK2 should be performed with at least one day (24h) in between and Visits 4, PK3 and PK4 should also be performed with at least one day in between.

[s] The Investigational Medicinal Product (IMP; ARGX-113 or placebo) will be administered as an intravenous (IV) infusion over a period of 1 hour at Visits 1, 2, 3, and 4. The first 5 Japanese patients need to be hospitalized for 24 hours after the end of the 1st infusion of IMP (see also Section 4.2 of the protocol). Subsequent patient will remain at the site for at least 1 hour following the end of the infusion for safety monitoring based on the patient's clinical status.

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

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

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

IMP administration during the trial. Patients who discontinue early from randomized treatment in the ITC period will have to complete the EoT assessments and then continue into the Safety and Disease Severity Follow-up period as per table 2 of the protocol.

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

[x] Day 182 or 6th April 2020, whichever comes first.

[y] If Visit 9 falls on 6th April 2020 then there is no permissible window and this visit must occur at the latest on 6th April 2020.

Schedule of Assessments for Patients who Discontinued Early from Trial Treatment[a]

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

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

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

[b] After the patient completed either the current Treatment Cycle or the EoT assessments of the current ITC visit if decision was made in the ITC period, the patient should return every month for the Safety and Disease Severity Follow-up visits until Day 182 or 6th April 2020, whichever comes first, as per this SoA.

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

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

[e] Disease severity assessments should be performed prior to any other trial-specific assessment in the following sequence: 1) MG-ADL, 2) QMG. Acetylcholinesterase inhibitors must be halted for at least 12 hours before the QMG assessment (consistent with the revised manual for the QMG test as recommended by the Myasthenia Gravis Foundation of America Inc [MGFA]).

[f] A urine pregnancy test will be performed only for women of childbearing potential (see definition of terms of the protocol)

[g] Day 182 or 6th April 2020, whichever comes first.

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Reason for signing: Approved	Name: PPD Role: S Date of signature: 08-May-2020 09:57:53 GMT+0000
Reason for signing: Approved	Name: PPD Role: P Date of signature: 08-May-2020 10:04:10 GMT+0000
Reason for signing: Approved	Name: PPD Role: P Date of signature: 11-May-2020 06:09:23 GMT+0000
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