Protocol ARGX-117-2002

A Phase 2, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group, Multicenter Trial to Evaluate the Safety and Tolerability, Efficacy, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of 2 Dose Regimens of ARGX-117 in Adults With Multifocal Motor Neuropathy

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Phase:	2
Methodology:	Randomized, Double-Blinded, Placebo-Controlled
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SIGNATURE PAGE

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.
I have discussed any questions I have regarding the contents of this document with the biostatistical author.
I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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MODIFICATION HISTORY

Current Version	Date	Amended by	Summary of Changes from previous version	Reason
1.0	24-Nov-2023			
2.0	25-APR-2024	[redacted]	Section 3.2, 6.5.1.2, 6.5.1.3 and 7: The following endpoints were removed: - Proportion of participants showing a deterioration of 1 or more points in at least 2 muscle groups as assessed by the mMRC-14 sum score - Proportion of participants with no deterioration in 2 or more muscle groups as assessed by mMRC-14 sum score - Proportion of participants with a GS decrease of 8 kilopascal (kPa) or more over 3 consecutive days of GS daily average	[redacted]
			Section 5.2 End of Treatment Visit for participants who are on-going in the DBTP at the data cut-off date is the last administration date	Add definition of end treatment visit for participants who are on-going in the DBTP

6.1.2.3: Worst post baselines assessment will be derived for DBTP and overall	Worst post-baseline during SFU not needed for the analysis.
Section 6.3.1 Period duration listing was removed	argenx standard
Section 6.4.1 Listing of TEAE leading to Interruption of IMP	argenx standard
Section 6.5.1.1 For time to the first retreatment with IVIg and Time to relapse analysis, the following censoring rule was added survival If the participant is ongoing in cohort 2, the censoring date will be the date of the data cutoff date	Add a censoring rule for cohort 2 as subjects will be on-going during DBTP at the time of the analysis
Section 6.5.1.1 Sentence added: If the stop date of last IVIg treatment before randomization is missing then the start date will be used.	Add rule for subject with no stop date of last IVIg treatment

Section 6.5.1.1 The total number of IVIg administrations will be derived	Add new variable
Section 6.5.3: The variable Number of scheduled hours was added.	New variable
Section 6.5.3 Derivation of Hours lost due to presenteeism was corrected to Hours lost due to presenteeism= [(Scheduled hours - Hours missed form work) x (impact/100)]	Error in Derivation of Hours lost due to presenteeism
[redacted]	[redacted]
Section 5.3: For interim analysis 2 and final analysis, data will be presented first by cohort and then by total placebo	Analysis by cohort will be presented to have the randomized comparison for each cohort.

	Section 6.3.1 and 6.3.2: Summary data presented for each cohort by treatment group and overall.
	Section 6.2.1: results will be presented first by cohort and then by total placebo (combined placebo from cohort 1 and 2) instead of In the outputs, results will be presented first by cohort and then by total placebo. For Immunogenicity, results will be presented by active treatment for each cohort, Total active treatment group and Total Placebo. A total column may also be added
	Section 6.2.1: For the analysis of continuous endpoints, each ARGX treatment group will be compared to the placebo group of the respective cohort.
Section 5.5 Add analysis visit window for PK and PD	Analysis visit windows defined according to argenx standard
Section 6.5.1.2: for all mMRC endpoints 95% CI and common risk differences were removed.	Removed Statistical parameters

	Section 6.2.1: Descriptive statistics for PD ~~parameters~~ serum concentrations will include the number of non missing data points , the arithmetic mean, the SD, the SE, the 95% CI, the median, minimum, Q1, Q3, and maximum.	Clarification
	Section 6.2.1.2 and 6.5.1.3: For GS daily Average and GS 3-day Moving Average, the ANCOVA will be performed the change from baseline. In SAP v1.0, ANCOVA were planned to be performed on the percent change from baseline.	Change of the ANCOVA analysis for GS daily average and GS 3-day Moving Average. ANCOVA performed on the percent change from baseline are more affected by extreme outliers than the change from baseline
	Section 6.2.1.2 and 6.5.2: ANCOVA for the change from baseline of the CAP-PRI total score were added.	New analysis
	Section 6.2.1.4 Samples taken the day or after an important PD that may impact the interpretability of the PK/PD will be excluded from the PK/PD analysis". For this , the date of the deviation in DV should be considered.	Add new section for selection of samples for PK/PD

	Section 6.3.6 A summary of Baseline scores were added for main efficacy endpoints.	Add summary table for scores at baseline
	Section 6.6.1 For Pharmacokinetics, AUC_{0-t}, AUC_{∞}, $t_{½}$, V_z, CL, Cmax/Dose will not be derived	PK parameters removed due to the small number of subjects who entered into the Safety Follow-up period
	Section 6.6.3 For immunogenicity, Frequency tables will not be presented by placebo cohort 1, placebo cohort 2 and overall.	Placebo group will not be presented for immunogenicity data
	Section 9.2: Summary of ANCOVA table for CAP-PRI Total Score were added (14.2.1.55 and 14.2.1.56).	Update due to the new analysis mentioned above (ANCOVA of the CAP-PRI total score)
	Section 6.2.1 For efficacy and safety tables by analysis visit, only analysis visits with at least 15 participants (overall) will be shown.	Specify that this rule is applicable for efficacy and safety tables only.
	6.2.2 The name of the treatment groups was changed from ARGX-117 to Empasiburart and Placebo to Total Placebo.	Update of the treatment group
	Section 6.2.3 definition of IVMP baseline and baseline	Correction of the definition of baseline for HRPQ

	for HRPQ was not corrected in the SAP v1.0: the questionnaire with at least one non missing item based on SDTM datasets for at least one item from HRPQ01 to HRP09 will be used for IVMP baseline instead of "all items from HRPQ01 to HRPQ09 based on SDTM datasets should be non missing at the selected date to be defined as baseline."	
	Section 6.3.2.5: Rule added for the derivation of the number of IVIg administrations during IVMP in case of unscheduled visits: If unscheduled visits are not on consecutive days, one unique IVIg administration should be counted per unscheduled visits. If unscheduled visits are performed on consecutive days, then IVIg administrations should be counted as a single administration".	Rule added for the derivation of the number of IVIg administrations during IVMP in case of unscheduled visits which was not correctly done in IA1.
	Section 6.3.2.5 Rule added for IVIg treatment during IVMP	Total IVIg dose in case of IVIg administrations performed over several days was done erroneously in IA1. Rule

		added for IA2. The table 14.1.1.13 is impacted.
	In case of IVIg administrations given on several days for a single visit, a unique record (e.g. first day) should be considered to determine the dose of IVIg administered at this visit. The total IVIg dose over the IVMP period is the sum of the unique doses associated to each visit, including unscheduled visits.	
	Section 6.3.3 If the end date is after the end of study date, end date will be imputed to end of study date.	Rule added for end date of concomitant medications or procedures after the end of study date.
	Section 6.3.5 The following sentence was added: For cohort 2, in the case of selection of dose regimen 3, for participants who received active treatment, administrations of placebo will be taken into account in the calculation of the dose related parameters (number of infusions, average duration for subsequent infusions, average dose for the	Add detail for the derivation of variable for the Dose regimen 3 active group

	subsequent infusions and cumulative dose)	
	Section 6.4.2 A listing of Laboratory results will be provide for abnormailities or Toxicity Grade ≥ 1	argenx standard
	Section 6.4.2 In case of multiple titers results for the same assessment, the worst assessment (ie the most positive) should be considered.	New sentence added to cover cases with multiple titers results for a same assessment
	Section 6.4.3 For vital signs, Treatment emergent category will added in the shift table	argenx standard
	Section 6.5.1.1 Rule added If unscheduled visits are performed on consecutive days during treatment period, then IVIg administrations performed on these consecutive days should be counted as a single administration. For the IVIg dose associated to this single administration, the first record will be selected. The total IVIg dose over the treatment period is	Total IVIg dose in case of IVIg administrations performed over several days was done erroneously in IA1. Rule added for IA2. The table 14.2.1.5 is impacted.

	the sum of doses over all single IVIg administrations.	
	Section 6.5.1.3: For GS, listings will be provided for IVMP baseline, last assessment during IVMP, baseline, last assessment during DBTP and last assessment before IVIg and not for on-site visits.	Change of GS listings
	Section 6.5.2: ANCOVA were removed for 9-HPT.	Statistical analysis removed for 9-HPT
	Section 6.5.2 Percent change from IVMP baseline and percent change from baseline will be derived for 9-HPT.	New summary statistics
	Section 6.6.1: add the following sentence: Listings will always present BLQ.	Clarification on the display of PK results
	Section 6.6.2 Add rule for the PD value above the quantification limit Safety and PD values expressed as below **(or above)** the quantification limit will be imputed by the value of the quantification limit itself. For participants with a baseline PD	argenx standard

	value below**/above** the quantification limit, the PD parameter will be excluded from the statistical analysis involving change and percent change from baseline.	
	Section 6.6.3 For immunogenicity analysis, the survival analysis of the time to the first retreatment with IVIg by Overall Antidrug Antibodies Participant Classification was removed .	Analysis removed due to small sample size
	Section 6.5.4: [redacted]	[redacted]
	Section 6.6.1 PK parameters listing was removed.	Not needed as individual PK parameters are provided in table
	Section 3.2 and 6.6.2: For Free C2, CH50 and C2, the maximum percent change from baseline was added	Additional summary statistics tables for free C2, CH50 and C2

	For free C2 and CH50, maximum decrease from baseline and minimum post baseline value were added For total C2, the maximum increase from baseline, maximum post baseline value during DBTP was added	
	Section 6.4.5 Shift table of ANA categories from baseline versus Baseline during DBTP and Safety Follow-up was added.	Shift table added
	Section 6.5.5 Addition of two efficacy summary tables: Summary of Efficacy Parameters at last assessment DBTP prior to IVIg retreatment by IVIg retreatment– Safety Set Summary of Efficacy Parameters at last assessment DBTP prior to IVIg retreatment by PGIC category – Safety Set	Addition of efficacy summary tables
	Section 6.6.2 Pharmacodynamic listing was removed	Not needed as individual data are provided in table

	Section 6.7.1 Complement factors listing was removed	Not needed as individual data are provided in table
	Section 7.2: Definition of specific AEs was updated: Table 6: change of the definition of local reaction to Any AEs with MedDRA PT in the MedDRA High Level Group Term of administration site reactions, regardless of time of onset instead of any AEs with HLT-Infusion site reaction instead of "Any AE with "Is this an adverse event of special interest" = Yes in the CRF "Adverse event" page?" (SAP v1.0) Table 6: change of the definition of AESI to AESIs are defined as events with grade ≥ 3 and a PT that falls under the MedDRA SOC Infections and infestations instead of "Any AEs" with "Is this an adverse event of special interest" – Yes on the eCRF Adverse event page (SAP v1.0)	Change of the derivation of AE for local reaction and AESI to align with argenx standard analysis.
	Section 9.2 Update the list of Tables, Figures and Listings for interim analysis 2	Update list of tables

		Section 5.5, 6.6.1 and 6.6.2: add visit window for PK and PD	Visit window
3.0	12-JUL-2024	Section 6.6.2 LLOQ values for the imputation rule for PD values below the quantification limit added. Imputation rule for PD values above the quantification limit added: PD values expressed as above the quantification limit will be imputed by maximum value of PD parameter or ULOQ itself, if available.	LLOQ and ULOQ values for pharmacodynamic parameters were missing for IA2.
		Section 5.5 For PK and PD visit windows: add rules for multiple assessments within the same visit window. Sentence added: The pre-dose sample should only be slotted if the treatment received at the previous IMP administration is as planned.	Rules for multiple assessments for PK and PD and pre-dose sample were specified in the Note to File “Rules for PK/PD visit windows in ARDA SAP v2.0”, 06-MAY-2024. These rules are integrated in the SAP v3.0.
		Section 6.4.2	argenx standard

		Change of definition of Treatment-emergent toxicity grade: Treatment-emergent toxicity grade values are defined with laboratory values with higher grade post-baseline compared to the grade at baseline. If baseline is missing any postbaseline toxicity will be considered treatment-emergent. In SAP v2.0, the definition is: Treatment-emergent toxicity grade values are defined as laboratory values with grade 0 at baseline and grade from 1 to 4 at any post-baseline visit. Section 6.4.3 and 6.4.4	
		Treatment emergent out of range values a are defined as follows: Treatment-emergent out-of-range values are defined as follows: - with normal values at baseline and low or high value at any post baseline visit, or - with low values at baseline and high at any post baseline visit, or	argenx standard

		- with high values at baseline and low at any post baseline visit. If baseline is missing any postbaseline abnormality will be considered treatment-emergent.	
	Section 6.4.4	Add definition of treatment-emergent abnormality for QTc parameters: a treatment-emergent abnormality is defined as any postbaseline abnormality which was not present at baseline or which worsened following baseline (eg, QTcF]450; 480] ms at baseline and>500 ms postbaseline). If baseline is missing any postbaseline abnormality will be considered treatment-emergent. Add shift table for QTc Parameters Add summary table for QTc Change Section 6.7.1	argenx standard

[redacted]

[redacted]

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ABBREVIATIONS

Abbreviation	Definition
ADA	Antidrug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification System
$AUC_{0\text{-last}}$	AUC from time zero to time t of the last measured quantifiable concentration
$AUC_{0\text{-72h}}$	Area under the concentration versus time curve from 0 to 72 h
$AUC_{0\text{-168h}}$	Area under the concentration versus time curve from 0 to 168 h
$AUC_{0\text{-336h}}$	Area under the concentration versus time curve from 0 to 336 h
AUC_{∞}	Area under the concentration versus time curve from 0 to infinity
BLQ	Below Limit of Quantification
CI	Confidence Interval
C_{max}	Maximum observed serum concentration
C_{168h}	Concentration at 168 h
C_{336h}	Concentration at 336 h
CL	Total clearance after first dose and at steady state
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DBTP	Double-Blind Treatment Period
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
ED	Early Discontinuation
EDRT	Executive Data Review Team
ENR	Enrolled Set
FSS	Fatigue Severity Scale

Abbreviation	Definition
GS	Grip Strength
HRPQ	Health-Related Productivity Questionnaire
iAUC	incremental Area Under the Curve
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IVDP	IVIg Dependency Period
IVMP	IVIg Monitoring Period
IVRS/IWRS	Interactive Voice/Web response System
LLOQ	Lower Limit Of Quantification
LTE	Long-Term Extension
MCC	MMN Confirmation Committee
MedDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal Motor Neuropathy
mMRC	Modified Medical Research Council
PYFU	patients' year of follow-up
PGIC	Patients' Global Impression of Change
PK	Pharmacokinetics
PD	Pharmacodynamics
PT	Preferred Term
PHQ-9	Patient Health Questionnaire
SAF	Safety Set
SAFFU	Safety Follow-up Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
$t_{½}$	apparent terminal half-life
TSQM-14	Treatment Satisfaction Questionnaire for Medication
ULOQ	Upper Limit of Quantification

Abbreviation	Definition
VAS	Visual Analog Scale
V_z	volume of distribution after first dose and at steady state
WHO	World Health Organization
9-HPT	Nine Hole Peg Test

1 INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1 Introduction

This is a phase 2, randomized, stratified, double-blinded, placebo-controlled, parallel-group, multicenter trial to evaluate the safety and tolerability, efficacy, Pharmacokinetics (PK), Pharmacodynamics (PD), and immunogenicity of 2 dose regimens of ARGX-117 in adults with multifocal motor neuropathy (MMN).
This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of trial data to answer the study objective(s). Analysis sets, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this trial.
This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2 Objectives

The objectives of the study ARGX-117-2002, as stated in the protocol, are:

Primary objective:

- To evaluate the safety and tolerability of ARGX-117 compared with placebo in adult participants previously stabilized with IVIg. The primary endpoints are adverse events (AEs), clinical laboratory variables, vital signs, concomitant medications, and suicidal behavior

Secondary objectives:

- To evaluate the efficacy of ARGX-117 compared with placebo on muscle strength and/or motor function in adult participants previously stabilized with IVIg based on:
  - Time to the first retreatment with IVIg since the final IVIg treatment of the IVIg monitoring period
  - Time to relapse
  - Modified Medical Research Council (mMRC) score that evaluate motor strength/weakness from predetermined muscle groups assessments
  - Grip strength (GS) assessments
- To evaluate the efficacy of ARGX-117 on functional ability, arm and hand function, quality of life, and fatigue in adult participants with MMN
- To evaluate the effect of ARGX-117 on health-related productivity and work productivity using Health-Related Productivity Questionnaire (HRPQ)
- To evaluate treatment satisfaction
- To assess the PK, PD, and immunogenicity of ARGX-117

Exploratory objectives:

[redacted]

[redacted]

1.3 Scope of the SAP

This SAP details statistical analysis specified in the Protocol ARGX-117-2002, 4.0, amendment number 3, 02 March 2023.

This SAP covers all analyses relative to the objectives described in section 1.2 except the following:

- [redacted]
- [redacted]

[redacted]

2 STUDY DESIGN

2.1 Introduction

ARGX-117-2002 is a randomized, double-blinded, placebo-controlled, parallel-group, multicenter trial to evaluate the safety and tolerability, efficacy, PK, PD, and immunogenicity of 2 dose regimens of ARGX-117 in adults with MMN.

The total trial duration is, at minimum, 25 weeks for all participants.

Two cohorts of at least 24 participants each will be enrolled in a sequential fashion.
The first cohort will assess dose regimen 1 [redacted]. An independent data monitoring committee (IDMC) will conduct a review of the accumulated data. At least, 3 meetings will be held. In particular, data collected when the first 9 participants in cohort 1 have completed or early discontinued the Double-Blind Treatment Period (DBTP) will be evaluated by the IDMC. The IDMC will make recommendations and will inform the unblinded executive data review team (EDRT) on the recommendations on continued dosing within a cohort, the opening of cohort 2, and modification or discontinuation of the trial. The EDRT will decide to open cohort 2, and if applicable, the selection of the final dose regimen option. [redacted]

For both cohorts, there will be a screening period, an IVIg dependency period (if applicable), an IVIg monitoring period, a DBTP, and a safety follow-up period.

Screening Period

All participants will begin with a screening period. The individual's eligibility to participate in the trial will be assessed. The diagnosis of MMN will be confirmed by the MMN Confirmation Committee (MCC) to be eligible. IVIg dependency will be assessed by the MCC as well.

Participants whose IVIg dependency is uncertain will enter an IVIg dependency period. Participants whose IVIg dependency is certain will enter directly in an IVIg monitoring period.

The screening period will occur for up to 28 days and may be extended by an additional 14 days to a total of 42 days with the written approval of the medical monitor.

IVIg Dependency Period (IVDP)

Participants whose IVIg dependency is uncertain based on the MCC will enter an IVIg dependency period to assess the impact of a delayed IVIg administration on GS and/or motor function.
Participants will receive IVIg following a delayed administration schedule compared to their stable IVIg regimen interval. Frequency of visits during the IVDP is:

- Participants receiving IVIg every 2 weeks will extend the interval to 4 weeks
- Participants receiving IVIg every 3 weeks will extend the interval to 6 weeks
- Participants receiving IVIg every 4 weeks will extend the interval to 8 weeks
- Participants receiving IVIg every 5 weeks will extend the interval to 10 weeks

Participants will have an earlier visit than planned during the IVDP if a participant demonstrates a clinically meaningful deterioration between the scheduled visits of the IVDP. [redacted]
The IVDP will last up to 15 weeks (105 days) depending on the IVIg dose frequency.

IVIg Monitoring Period (IVMP)

The IVMP will begin after the participant has completed the screening period and the IVDP (if applicable), and will consist of multiple administration cycles of IVIg.
This period will establish baseline values for all clinical endpoints assessed during the DBTP.

- Participants will receive IVIg at the frequency, duration, and dose described in their medical history

- The IVMP includes 3 IVIg treatment cycles

- The length of the IVMP will depend on an individual's IVIg dose frequency, as follows:
  - Dosed every 2 weeks: 35 days
  - Dosed every 3 weeks: 49 days
  - Dosed every 4 weeks: 63 days
  - Dosed every 5 weeks: 77 days

The length of the IVMP may be greater if a participant receives IVIg over the course of several days.

Double-Blinded Treatment Period (DTBP)

For each cohort:
The dosing of IMP will begin at V1 and continue throughout the DBTP.

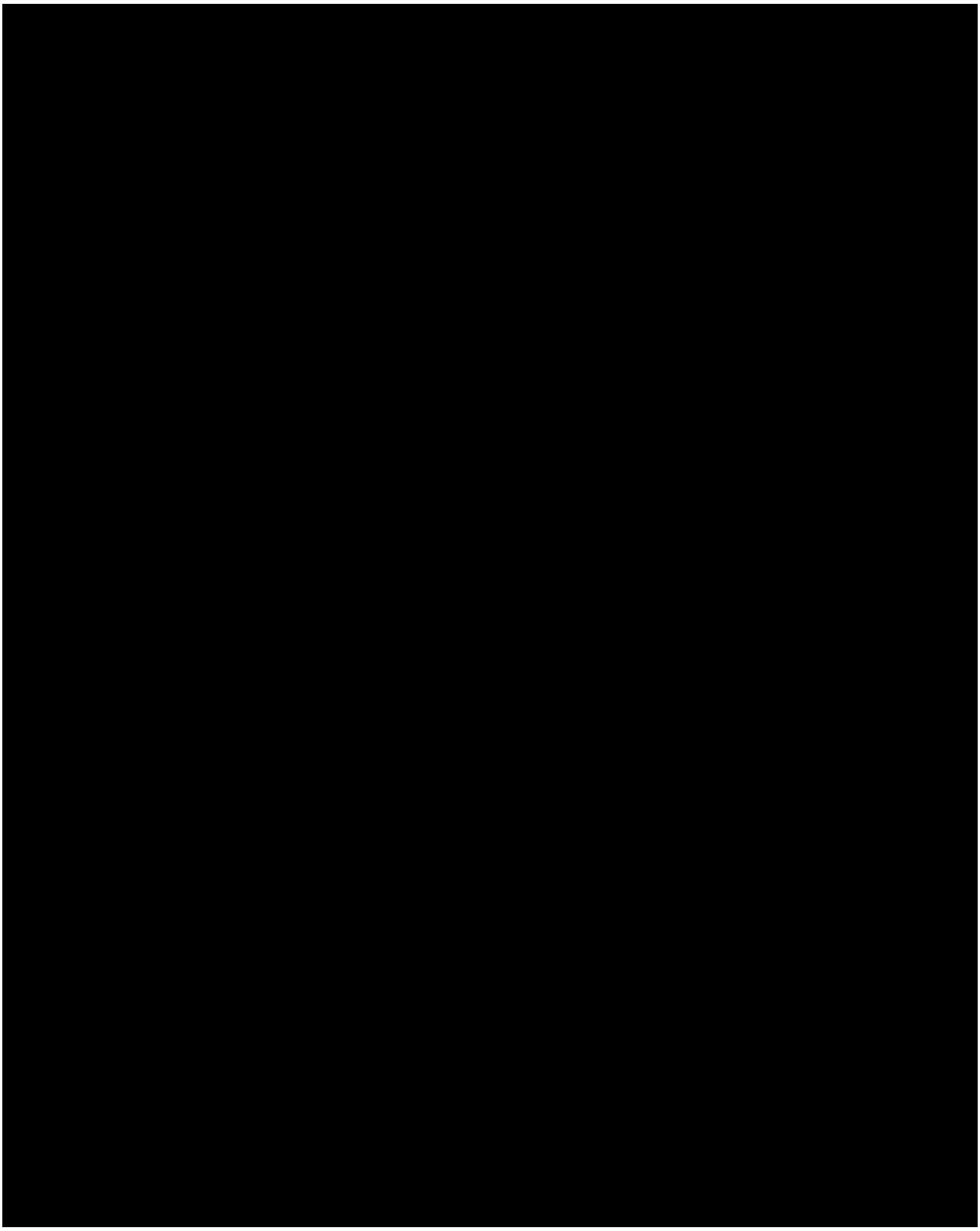
- The DBTP will begin 7 days after the final IVIg administration of the IVMP

- Participants will be randomized at day 1 of the DBTP (Figure 1):
  - [redacted]
  - [redacted]
    - Randomization will be stratified based on an individual's IVIg dose frequency as described in Section 2.2.
- For cohort 2, the dose regimen chosen by the EDRT will remain blinded to the participant, investigator, and the sponsor's study team to avoid any bias in the outcome assessments.
- Participants will be treated with IVIg during the DBTP if there is a clinically meaningful deterioration in muscle strength and/or motor function. [redacted]
  - Administration of IMP will not be paused/stopped when IVIg retreatment is initiated
  - Based on their clinical judgment, the investigator may choose to not re-treat the participant with IVIg in the event of a clinically meaningful deterioration
  - All study participants can request IVIg retreatment with the investigator anytime during the DBTP.

The following interim database locks will occur:

- After the completion of the 16-week DBTP by all participants included in cohort 1. Only participants from cohort 1 will be unblinded
- After the completion of the 16-week DBTP by the 24th participant included in cohort 2. The second interim analysis will include all participants included in cohort 2 and all participants of cohort 2 will be unblinded, even ongoing participants.

A final database lock will occur when all participants have completed the safety follow-up period, or have rolled over to the long-term extension (LTE) study, if applicable.

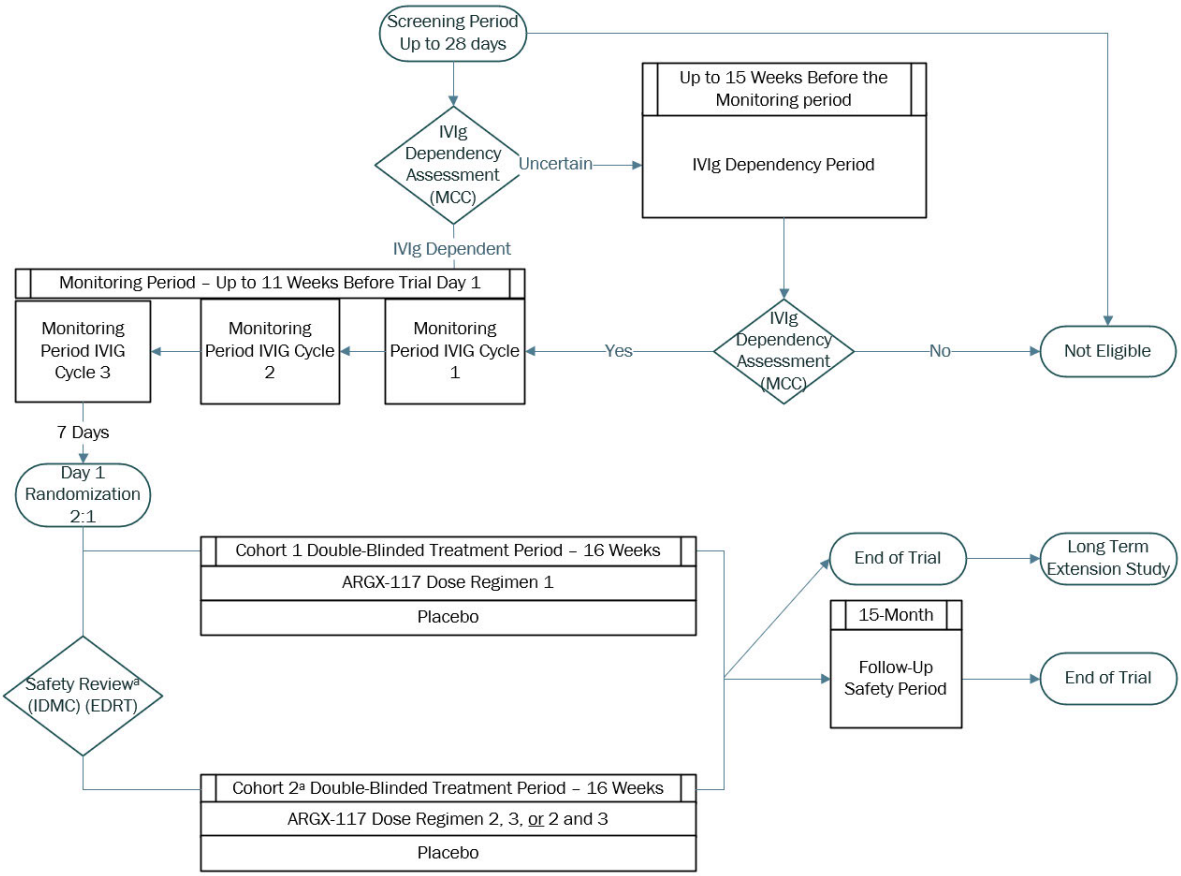


Safety Follow-up Period

After completing the 16-week DBTP, participants may enroll in an LTE study (which is not part of ARGX-117-2002) and continue to receive ARGX-117; otherwise, participants will enter the safety follow-up (SFU) period (without ARGX-117 treatment). The safety follow-up period will characterize safety, PK, and PD during the elimination of ARGX-117. The SFU period will begin after the DBTP and will continue for at least 15 months; the day of the first SFU visit will be considered the start of the SFU period.

A schematic of the study design is shown in Figure 2. The schedule of activities is in appendix 9.1, further details are available in the study protocol.

Figure 2 Study Design



EDRT=executive data review team; IDMC= independent data monitoring committee; IVIg=intravenous immunoglobulin; MCC=MMN confirmation committee; MMN=multifocal motor neuropathy
Note: An IVIg cycle is 1 administration of IVIg.

[redacted]

Sample Size and Power

This is an exploratory study, no formal sample size calculation was made, and no formal hypothesis testing will be performed. A total of 48 participants (16 per treatment arm) are planned to be randomized, which is considered sufficient to respond to the primary objective (refer to Section 6.1).

2.2 Randomization Methodology

In this randomized controlled trial, for each cohort, 24 participants will be randomized using an interactive voice/web response system (IVRS/IWRS).

Participants will be randomized on day 1 of the DBTP:

- In a 2:1 ratio to ARGX-117 or placebo in cohort 1, and for option 1 ([redacted] or option 2 [redacted] in cohort 2
- In a 2:2:1:1 ratio to ARGX-117 [redacted] ARGX-117 [redacted] placebo [redacted], or placebo [redacted] for option 3 in cohort 2

Participants will be randomized on day 1 of the DBTP: [redacted]

2.3 Stopping Rules

The trial shall be immediately suspended, and an urgent referral made to the IDMC for expedited advice if the stopping rules described in the protocol v4.0 are met.

2.4 Blinding

This is a double-blinded trial in which the investigator, study nurse/coordinator, participant, the sponsor's designated contract research organization (CRO), and sponsor study team are blinded to study intervention during the entire DBTP even if the participant withdraws from the study or enters the LTE.

For the conduct, analysis and monitoring of the trial, some study staff are unblinded to treatment assignment:

- clinical study pharmacy staff, due to the difference of viscosity between placebo and ARGX-117
- an unblinded clinical study supply manager
- an unblinded Clinical Research Associate who will monitor pharmacy
- an unblinded data manager who will have access to unblinded data (eg, PK) for data cleaning reconciliation
- an unblinded independent statistician from IRT vendor who will prepare and have access to the randomization code

Although unblinded to treatment assignment, none of the above roles will have access to unblinded summaries of efficacy or safety data.

The IDMC will have access to unblinded safety and efficacy data reports to discharge their roles for data analysis and review during IDMC meetings. These reports will be prepared by the unblinded independent IDMC support statistician.
The unblinded EDRT, composed of senior executive members from the sponsor, will have access to unblinded data for the purpose of strategical decision making and planning.

[redacted]

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Safety variables include AEs, clinical laboratory variables, vital signs and suicidal behavior.

3.2 Secondary Efficacy Endpoints

- **IVIg retreatment**
  - Time to the first retreatment with IVIg since the final IVIg treatment of the IVMP
  - Time to relapse
  - Number of participants retreated with IVIg
  - Number of IVIg administrations during DBTP
  - Total IVIg dose (g/kg)
  - Average IVIg dose / week (g/kg)
  - Average IVIg dose interval (weeks)

- **Endpoints derived from modified Medical Research Council (mMRC) scores:**
  - **mMRC-10 sum score**
    - Value and change from baseline in mMRC-10 sum score
    - Net incremental Area Under the Curve (iAUC) per week of the change from baseline in mMRC-10 sum score
    - Proportion of participants showing a deterioration of at least 2 points as assessed by the mMRC-10 sum score
- **mMRC-14 sum score**
  - Value and change from baseline of mMRC-14 sum score
  - Value and change from baseline in the average of the mMRC-14 sum score for the 2 most important muscle groups

- **Endpoints derived from GS:**
  For each hand (the most affected and the less affected hand):
  - Value, change from baseline, percent change from baseline and maximal percent change from baseline of GS daily average
  - Net iAUC per week of the change from baseline of GS daily average
  - Value, change from baseline, percent change from baseline of GS 3-day moving average
  - Proportion of participants with > 30% reduction from baseline over 2 consecutive days of GS 3-day moving average

- **Endpoints to assess functional ability, arm and hand function, quality of life, and fatigue**
  - MMN-RODS
    - Values and change from baseline in MMN-RODS centile metric score
    - Values and change from baseline in MMN-RODS raw score

- 9 Hole Peg Test (9-HPT)
  For each hand (dominant / non dominant)
  - Values, change from baseline and percent change from baseline in average time (seconds)
- EQ-5D-5L
  For each dimension (Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression):
  - Proportion of participants by level of severity

  For the health state VAS:
  - Value and change from baseline
- CAP-PRI
  - Values and change from baseline in CAP-PRI total score
- Patients' Global Impression of Change (PGIC)
  - Proportion of participants by level of improvement
- Fatigue Severity Scale (FSS)
  - Values and change from baseline in the FSS total score

- **Endpoints to assess health-related productivity and work productivity**
  - Health-Related Productivity Questionnaire (HRQP)
    - Value at each visit:
      - Hours lost due to absenteeism
      - Hours lost due to presenteeism
      - Total hours lost (absenteeism and presenteeism)
      - Percent of scheduled hours lost due to absenteeism
      - Percent of scheduled hours lost due to presenteeism
      - Percent of total scheduled hours lost (due to absenteeism and presenteeism)

    These endpoints will be derived for work-related activities and household chores activities.

- **Endpoints to assess medication treatment satisfaction**
  - Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM-14)
    For each subscale (Effectiveness, Side effects, Convenience, Overall Satisfaction)
    - Value at each visit of the subscale score

- **Endpoints to assess PK, PD and immunogenicity**

  Serum concentrations and PK parameters for ARGX-117: AUC_{0-t}, AUC_{72h}, AUC_{0-168h}, AUC_{336h}, AUC_{∞}, C_{max} , C_{72h}, C_{168h}, T_{max}, $t_{½}$, V_z and CL

  Values, change from baseline and percent change from baseline, maximum percent change from baseline, maximum decrease from baseline (applicable for free C2 and CH50 only), minimum post baseline value(applicable for free C2 and CH50 only), maximum increase from baseline, maximum post baseline value (applicable for Total C2 only) in free C2, total C2, functional complement activity (CH50) over time

- Incidence and prevalence of antidrug antibodies (ADA) against ARGX-117

[redacted]

4 ANALYSIS SETS

4.1 Analysis Set Definitions

The following data sets will be used for the statistical analysis:

Enrolled (ENR) Set: all participants who signed an informed consent to participate to the trial
Note: Having signed an informed consent is defined as having a complete date for consent signature in the database.

Safety (SAF) Set: All enrolled participants who were randomized and received at least 1 dose, or part thereof, of IMP (ARGX-117 or placebo). Participants will be analyzed according to the treatment they received.

PK Set: All participants in the SAF and for whom at least 1 post dose serum PK concentration is available, excluding placebo participants.

PD Set: All participants in the SAF for whom at least 1 post-baseline value for PD parameter (including free C2, total C2 and CH50) is available

The SAF set will be used to analyze the primary safety analysis. The SAF will be used to analyze efficacy endpoints.

For analyses performed on the SAF, PK and PD sets, the actual treatment arm will be considered.

[redacted]
If a treatment switch or misallocation occurred, sensitivity analyses might be performed.

4.2 Protocol Deviations

Protocol deviations will be classified during monthly meeting as non important or important based on their effect on the rights, safety, or wellbeing of the participants and/or the quality and integrity of the data. The final rating will be confirmed on a blinded case-by-case basis prior to database lock (DBL).

Summaries of protocol deviations will be provided by class of deviation, overall and by treatment group in the SAF.

All protocol deviations will be listed.

5 DATA HANDLING

5.1 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 or Higher), unless otherwise noted. Medical History and adverse events will be coded using MedDRA version V24.1 - Sep 2021. Prior and concomitant medications will be coded using World Health Organization (WHO) B3 WHO Drug Global - Sep 2021 version.

5.2 Data Conventions

In the context of this SAP, 5 periods will be considered:

Screening period: from the date of signing informed consent to:

- For participants who enter the IVDP: the day prior to the first IVIg administration with 23:59 added
- For participants who enter directly the IVMP: the day prior to the first IVIg administration during IVMP with 23:59 added or if the participant discontinued during the screening period the date of study termination with 23:59 added as time part
- For participants who discontinued during the screening period: the date of study termination with 23:59 added as time part

IVIg Dependency period (IVDP): Only defined for participants with uncertain dependency to IVIg during screening: from the first IVIg administration date with 00:00 added as part time during IVDP to the day prior to the first IVIg administration with 23:59 added in IMVP or if the participant discontinued during the IVDP period the date of study termination with 23:59 added as time part

IVIg Monitoring period (IVMP): from the first IVIg administration date with 00:00 added as time part during IVMP to prior to the first IMP administration (time/date) -1 minute or if the participant discontinued during the IVMP period the date of study termination with 23:59 added as time part

Double Blind Treatment Period (DBTP):

- For the efficacy endpoints: From the first IMP administration date/time to V14 with 23:59 added as time part or date of early treatment discontinuation visit with 23:59 added as time part
- For AE and concomitant medication: From the first IMP administration date/time to:
    - Informed consent of LTE for participants who do enter into LTE. Date of informed consent corresponds to the treatment completion date in the main study. All data on the eCRF will be considered to belong to this period
    - 23h59 the day prior to the 1st FU visit at week 4 for those participants who do not enter into LTE or date of early study discontinuation with 23:59 added as time part if participant discontinued the study before FUV1
    - Date of study discontinuation with 23:59 added for participants who early discontinued study and do not enter in the safety follow up period

DBTP and Safety Follow-up period: For AE, from the first IMP administration date/time to:

- Informed consent of LTE for participants who do enter into LTE. Date of informed consent corresponds to the treatment completion/discontinuation date. All data on the eCRF will be considered to belong to this period
- Study discontinuation for those participants who do not enter into LTE

Participants who entered into LTE are participants who were eligible for LTE and signed the inform consent form.

Study Day 1 IDVP: The day of the first IVIg administration during IDVP

Study Day 1 IVMP: The day of the first IVIg administration during IVMP

Study Day 1: The day of the first administration of ARGX-117 or placebo

Study Day 1 FU: The day following V14/ED visit (D113) (for participants who do not enter into the LTE)

End of Treatment Visit: The V14 visit (D113) for participants who completed DBTP, or the visit following IMP discontinuation for participants who discontinue IMP prior to V14 (D113) or the last IMP administration date for participants who are on-going in the DBTP at the data cut-off date .

End of Study Visit: The V14 visit (D113) for participants entering the LTE, or the last recorded date in the DBTP or SFU period for participants not entering the LTE.

Scheduled or Unscheduled visits which do not fall into the visit windows will be listed, but not included in tables or graphs.

- **Conversion factors:**
  - 1 month = 30.4375 days
  - 1 year = 365.25 days
  - 1 week = 7 days
  - °C = (°F - 32)/1.8
- **Additional rules**
  - Weight values recorded in pounds will be converted to kilograms using the following formula: kilograms = pounds/2.2046.
  - Height values recorded in inches will be converted to centimeters using the following formula: centimeters = inches*2.54.
  - Duration on study (weeks) = (last visit date – informed consent date + 1) / 7.
  - Duration on treatment (weeks) = (last IMP intake date – first IMP intake date + 1) / 7.
  - Change from baseline = value at the time point – baseline value.
  - Percent relative change from baseline = [(value at the time point – baseline value) / baseline value] x 100.

5.3 Methods of Pooling Data

For the interim analysis 1, ARGX-117 dose regimen 1 and Placebo will be analyzed separately. For interim analysis 2 and final analysis, data from cohort 1 and cohort 2 will be presented separately, having a separate column for ARGX-117 and a column for placebo. In addition, a total column for placebo will be added, pooling participants who receive placebo either in cohort 1 or in cohort 2, forming a unique placebo arm.

5.4 Withdrawals, Dropouts, Loss to Follow-up

Discontinued participants who received the IMP will not be replaced.

Follow-up of participants who discontinued the IMP early will continue in the safety follow-up period until the last safety follow-up visit and the study procedures will be assessed per the schedule of activities (refer to section 9.1).

Withdrawal During Treatment period:
In case of early discontinuation during the treatment period, if possible, procedures at V14 should be conducted during an early discontinuation (ED) visit.

Withdrawal During Follow-up period:
In case of early discontinuation during the follow-up period, if possible, procedures of the last Safety Follow-up visit should be conducted during an ED visit.

5.5 Visit Windows

For safety, efficacy, PK, PD, immunogenicity [redacted], all visits (scheduled, unscheduled or early discontinuation) within a period will be mapped to an analysis visit as defined in Table 1 Table 2 and Table **3** where day 1 is defined as the first day within each period.

For GS (except for GS Net iAUC), only last analysis derived visits will apply (refer to 6.2.1.2). For GS Net iAUC, rules are described in section 6.5.1.3.

For PK and PD analyses, analysis windows for PK samples and PD samples (Free C2, total C2 and CH50) are defined in Table 4, Table 5, Table 6 and Table 7**.** The following considerations will have to be taken into account.

- Only the visits / timepoints defined per protocol will be considered for the analysis
- PK will be analyzed only for ARGX-117 treatment arms. Therefore, the previous or pre-previous IMP administration should refer to only active IMP administration. This implies that, in case of dose regimen 3, for which placebo administrations are planned, placebo administrations will not be taken into account.
- For PK, if the pre-dose sample is not slotted for an analysis visit, then post-dose samples should be excluded from the analysis
- For PK, in case of missing pre-dose sample, then the post-dose sample should be excluded.
- PD markers (Free C2, total C2 and CH50) are analysed for both empasiprubart and placebo treatment arms. In case of dose regimen 3, for empasiprubart arm, only active IMP

administration will be considered to define the window for the date of previous IMP administration. For consistency, for placebo arm of dose regimen 3, [redacted] will be considered for the date of previous IMP administration .

- For post-dose sample, the treatment received at the visit should be the one planned at the visit.
- The pre-dose sample should only be slotted if the treatment received at the previous IMP administration is as planned.

Per parameter and analysis window, the non missing value closest to the target day will be used in the analysis. If more than one non missing value is located at the same distance from the target day, then the one latest in time will be selected for analysis. The value latest in time will be identified using, in order of preference, the assessment time and the visit label.

For PK and PD, in case of multiple assessments within the window sample, the following rules will apply:

- For IVMP/IVDP: in case of multiple assessments per analysis visit / timepoint, the non missing value closest to the target day will be used in the analysis. Target day refers to the scheduled visit day (Table 4 and Table 5).
- During the DBTP, distinction needs to be made between pre-dose and post-dose samples:
    - For pre-dose samples, if more than one non missing value is located at the same distance from the target day, then the one latest in time will be selected for analysis (ie the closest to the IMP administration on this day)
    - For post-dose samples, in case of multiple assessments within the window sample, the closest assessment to the timepoint relatively to the start of the previous IMP administration will be selected.

Tables and listings will present the analysis visit window as defined below, not the eCRF visits. Allocations of assessments will be performed using their relative day within the period.

Table 1 Evaluation Intervals during the screening period and IVIg dependency period

IVIg Dosing Frequency	Protocol Scheduled Visit	Scheduled Visit Day (Relative Day during IVIg Dependency period)	Interval for Analysis Visit
	Screening		No analysis visit window
Q 2 weeks	IDV1	1	1
Q 3 weeks	IDV1	1	1
Q 4 weeks	IDV1	1	1
Q 5 weeks	IDV1	1	1
Q 2 weeks	IDV2	29	Day 2 to 23:59 on the day before IMV1

Q 3 weeks	IDV2	43	Day 2 to 23:59 on the day before IMV1
Q 4 weeks	IDV2	57	Day 2 to 23:59 on the day before IMV1
Q 5 weeks	IDV2	71	Day 2 to 23:59 on the day before IMV1

Table 2 Evaluation Intervals during the IVIg monitoring period

IVIg Dosing Frequency	Protocol Scheduled Visit	Scheduled Visit Day (Relative Day during IVMP)	Interval for Analysis Visit
Q 2 weeks	IMV1	1	1
Q 3 weeks	IMV1	1	1
Q 4 weeks	IMV1	1	1
Q 5 weeks	IMV1	1	1
Q 2 weeks	IMV2	15	Day 2 to Day 22
Q 3 weeks	IMV2	22	Day 2 to Day 32
Q 4 weeks	IMV2	29	Day 2 to Day 43
Q 5 weeks	IMV2	36	Day 2 to Day 53
Q 2 weeks	IMV3	29	Day 23 to end of IVMP (date/time of first IMP administration minus 1 minute)[1]
Q 3 weeks	IMV3	43	Day 33 to end of IVMP (date/time of first IMP administration minus 1 minute)[1]
Q 4 weeks	IMV3	57	Day 44 to end of IVMP (date/time of first IMP administration minus 1 minute)[1]
Q 5 weeks	IMV3	71	Day 54 to end of IVMP (date/time of first IMP administration minus 1 minute)[1]

[1] In case of assessment with time missing falling on date of first IMP administration, it will be allocated to IMV3.

Table 3 **Evaluation Intervals for safety and efficacy analysis during the DBTP**

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Table 4 Visit Windows for PD samples (free C2, total C2 and CH50) during IVDP

IVIg Dosing Frequency	Protocol Scheduled Visit	Scheduled Visit Day (Relative Day during the IDVP)	Protocol Window (days)	Timepoint	Window for sample
Q2 Weeks	IDV1	1	NA	Pre-dose	Assessment date/time before first IVIg administration
Q3 Weeks	IDV1	1	NA	Pre-dose	Assessment date/time before first IVIg administration
Q4 Weeks	IDV1	1	NA	Pre-dose	Assessment date/time before first IVIg administration
Q5 Weeks	IDV1	1	NA	Pre-dose	Assessment date/time before first IVIg administration
Q2 Weeks	IDV2	29	±7	Pre-dose	Date of previous IVIg administration + 28 days ± 7 days and performed before IVIg administration at this visit
Q3 Weeks	IDV2	43	±7	Pre-dose	Date of previous IVIg administration + 42 days ± 7 days and performed before IVIg administration at this visit
Q4 Weeks	IDV2	57	±7	Pre-dose	Date of previous IVIg administration + 56 days ± 7 days and performed before IVIg administration at this visit
Q5 Weeks	IDV2	71	±7	Pre-dose	Date of previous IVIg administration + 70 days ± 7 days and performed before IVIg administration at this visit

Table 5 Visit Windows for PD samples (free C2, total C2 and CH50) during IVMP

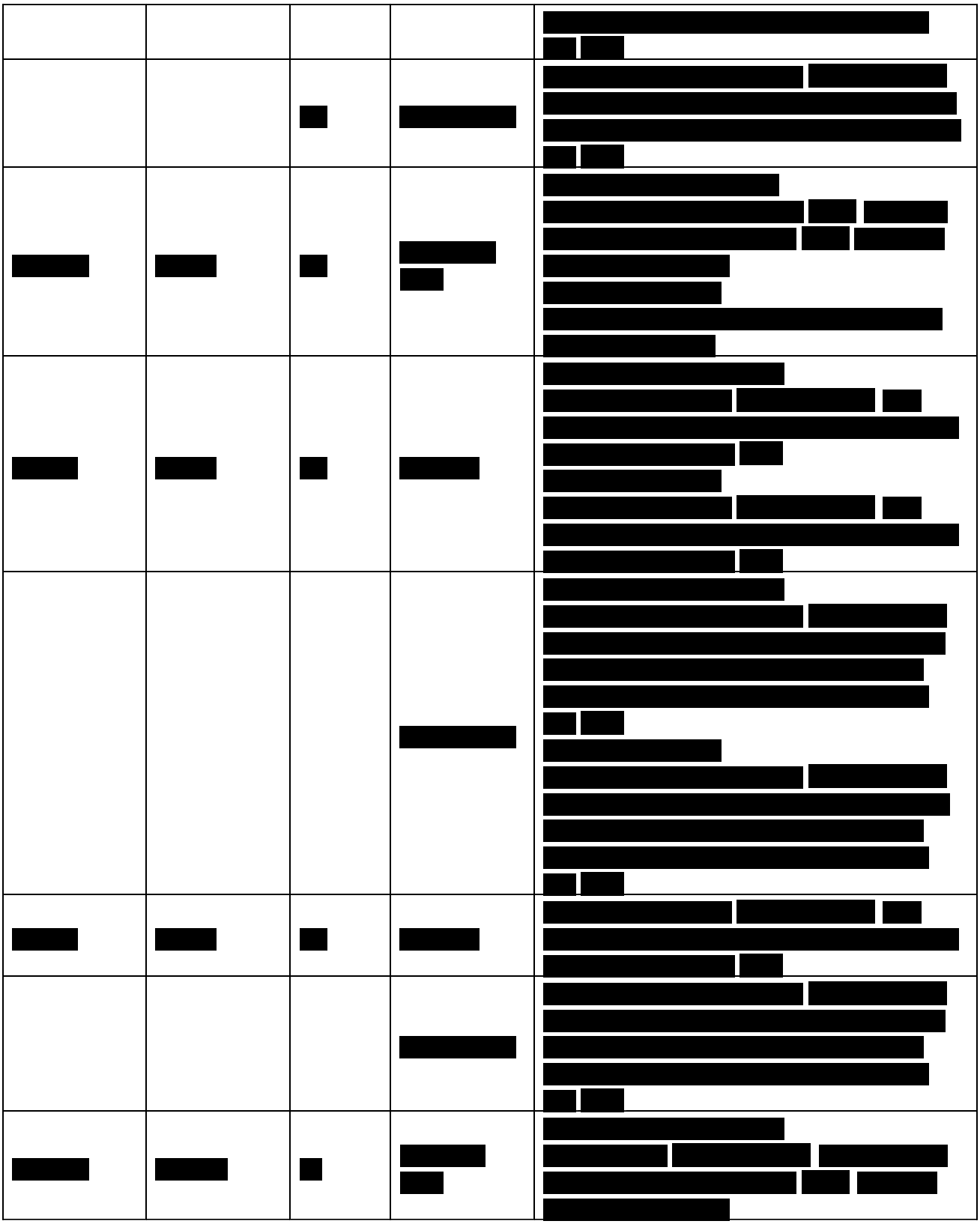
IVIg Dosing Frequency	Protocol Scheduled Visit	Scheduled Visit Day (Relative Day during the IMVP)	Protocol Window (days)	Timepoint	Window for sample**
Q2 Weeks	IMV1	1	NA	Pre-dose	Assessment date/time on or before first IVIg administration during IVMP
Q3 Weeks	IMV1	1	NA	Pre-dose	Assessment date/time on or before first IVIg administration during IVMP
Q4 Weeks	IMV1	1	NA	Pre-dose	Assessment date/time on or before first IVIg administration during IVMP
Q5 Weeks	IMV1	1	NA	Pre-dose	Assessment date/time on or before first IVIg administration during IVMP
Q2 Weeks	IMV2	15	±3	Pre-dose	Date of previous IVIg administration + 14 days ± 3 days and performed on or before IVIg administration at this visit
Q3 Weeks	IMV2	22	±3	Pre-dose	Date of previous IVIg administration + 21 days ± 3 days and performed on or before IVIg administration at this visit
Q4 Weeks	IMV2	29	±3	Pre-dose	Date of previous IVIg administration + 28 days ± 3 days and performed on or before IVIg administration at this visit
Q5 Weeks	IMV2	36	±3	Pre-dose	Date of previous IVIg administration + 35 days ± 3 days and performed on or before IVIg administration at this visit
Q2 Weeks	IMV3	29	±3	Pre-dose	Date of previous IVIg administration + 14 days ± 3 days and performed on or

					before IVIg administration at this visit
Q3 Weeks	IMV3	43	±3	Pre-dose	Date of previous IVIg administration + 21 days ± 3 days and performed on or before IVIg administration at this visit
Q4 Weeks	IMV3	57	±3	Pre-dose	Date of previous IVIg administration + 28 days ± 3 days and performed on or before IVIg administration at this visit
Q5 Weeks	IMV3	71	±3	Pre-dose	Date of previous IVIg administration + 35 days ± 3 days and performed on or before IVIg administration at this visit

Table 6 Visit Windows for PK during DBTP and Safety FU period

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]

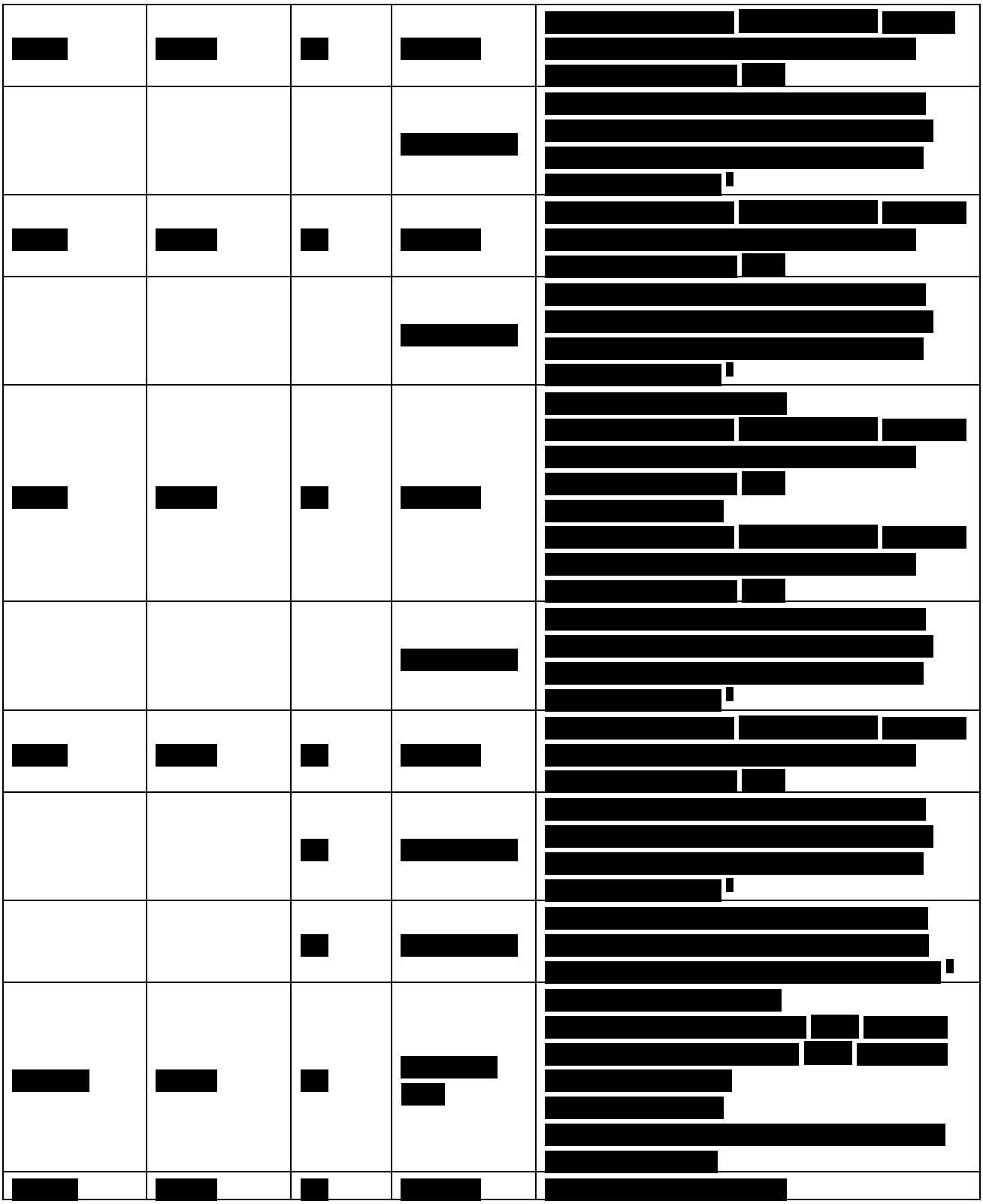
				[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]

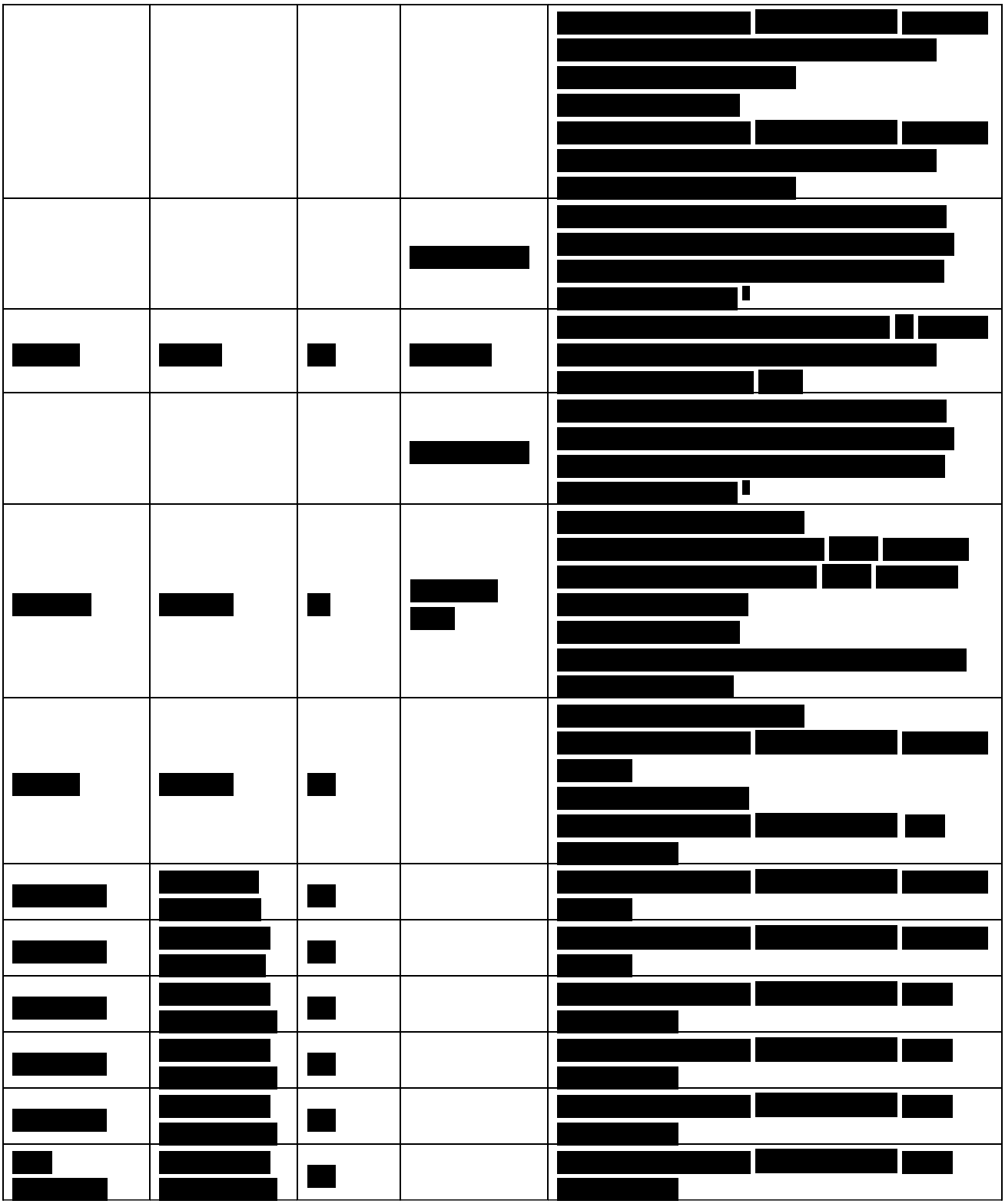


				[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]

[redacted]

Table 7 **Visit Windows for PD samples (free C2, total C2 and CH50) during DBTP and Safety Follow-up period**





[redacted]

6 STATISTICAL METHODS

6.1 Sample Size Justification

Given the exploratory nature of this study, no formal sample size calculation was made, and no formal hypothesis testing will be performed. A total of 48 participants (16 per treatment arm) are planned to be randomized, which is considered sufficient to respond to the primary objective.

6.2 General Statistical Methods

6.2.1 General Methods

All outputs will be incorporated into Word files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, safety, efficacy, PK and PD parameters, immunogenicity, complement factors and cytokines parameters.

For efficacy and safety tables by analysis visit (or analysis visit/timepoint), only analysis visits (or analysis/timepoint) with at least 15 participants (overall) will be shown.

In the outputs, results will be presented first by cohort and then by total placebo (combined placebo from cohort 1 and 2). For general characteristics, a total column will be added as the last column. Listings will be sorted by treatment arm and participant identifier. For Immunogenicity, results will be presented by active treatment for each cohort, Total active treatment group and Total Placebo. A total column may also be added (6.6.3).

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 will be shown.

For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented.

For continuous variables except for PK, PD and immunogenicity (described below), summary tabulations will be summarized using the following standard descriptive summary statistics: number of observations, number of missing observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. In addition, for efficacy measures, the SE and 95% CI will be provided.

Descriptive statistics for PD serum concentrations will include the number of non missing data points, the arithmetic mean, the SD, the SE, the 95% CI, the median, minimum, Q1, Q3, and maximum.

Descriptive statistics for PK serum concentrations [redacted] will include the number of observed values, arithmetic mean, SD, median, minimum and maximum, CV%, the geometric mean

(GM), and geometric CV% where geometric CV%=SQRT(exp(s^2)-1)*100 and *s* is the standard deviation of the log-transformed values. Serum concentrations will be reported as received by the bioanalytical laboratory.

Descriptive statistics for immunogenicity titer values will include the number of observed values, arithmetic mean, SE, 95% CI, median, Q1, Q3, minimum, maximum, the GM, and geometric CV%.

Mean, 95% CI, Q1, Q3, and median will be presented with one more decimal place than the measured values. SE and SD will be presented with 2 more decimal places than the measured values. Minimum and maximum will be presented with the same number of decimal places as the measured values.

For event-type safety data, the number and percentage of participants with an event will be shown. The denominator will be all participants in the analysis set per treatment arm.

For cross-tabulations, the denominator will be the number of participants in the analysis set per treatment arm. For tables where results are shown by analysis visit, the denominator will be the number of participants in the analysis set per treatment arm and analysis visit. Missing values will not be included in the denominator count when computing percentages. Percentages will be presented with 1 decimal place.

If a participant is re-screened, only data from the last screening will be displayed.

Data from the SFU period will be listed only.

6.2.1.1 eCOA data

The following efficacy assessments are reported using an electronic clinical outcome assessment (eCOA) platform or web portal: mMRC, GS, MMN-RODS, 9-HPT, EQ-5D-5L, CAP-PRI, PGIC, FSS, HRPQ, TSQM-14. In addition, C-SSRS and PHQ-9 are also assessed with the eCOA platform.

The Appendix 9.3 presents the derived variables directly computed by the eCOA platform. Some variables will be re-derived and used for the statistical analysis.

6.2.1.2 Efficacy analyses

For efficacy endpoints, descriptive summary tables will present the analysis visits and the 2 following last assessment derived visits:

- last assessment analysis visit during DBTP, defined as the last non missing post baseline value in the DBTP including the unscheduled visits
- last assessment before first IVIg retreatment analysis visit, defined as the last non missing post baseline value in the DBTP including the unscheduled visit, before the participant has been retreated with IVIg. Efficacy assessments performed on the day of retreatment of IVIg should be considered. In the case the participant has not been retreated with IVIg, last assessment available during the treatment period will be used.

These 2 derived visits are applicable for mMRC, MMN-RODS, 9-HPT, EQ-5D-5L, CAP-PRI, PGIC, FSS, HRPQ and TSQM-14. For HRPQ, the last available questionnaire with at least one non missing answer for all items from HRPQ01 to HRPQ09 (based on SDTM datasets) will be used.

For daily data for GS, descriptive summary tables will present the 3 following assessments:
- last assessment analysis visit during IVMP, defined as the last non missing post-IVMP baseline value, in the IVMP period including the unscheduled visits
- last assessment during DBTP, defined as the last non missing post baseline value during DBTP
- last assessment before first IVIg retreatment, defined as the last non missing post baseline value in the treatment period before the participant has been retreated with IVIg. Efficacy assessments performed on the day of retreatment of IVIg should be considered. In the case the participant has not been retreated with IVIg, last assessment available during the treatment period will be used.

Given the exploratory nature of the trial, there will be no formal hypothesis testing. Summary statistics, as well as 95% CIs on selected parameters, will be presented as described in the sections below.

For the analysis of continuous endpoints (including mMRC, MMN-RODS, CAP-PRI and GS), each ARGX-117 treatment group will be compared to the placebo group of the respective cohort.

[redacted]

For efficacy endpoints, exploratory analyses could be performed considering the longitudinal aspect of the data.

6.2.1.3 Worst post baseline

Post baseline worst-case analysis visit will be created for DTBP and overall for parameters with defined abnormalities and/or toxicity grades to summarize values considered as the worst-case. For abnormalities, the worst-case is derived per parameter, and if both the lowest and highest values are considered abnormal, a participant can have 2 worst-case analysis visits for the same parameter. For toxicity grades, the worst-case is the value associated with the highest toxicity grade and is derived per parameter and toxicity direction (decreased/increased).

For deriving worst post baseline value all non missing values will be considered included unscheduled visits.

6.2.1.4 PK/PD analyses

Samples taken on or the day the day of occurrence of an important protocol deviation that may impact the interpretability of the PK/PD will be excluded from the PK/PD analysis. Important protocol deviations that may impact the interpretability of PK/PD will be flagged in the SDTM database prior to DBL.

6.2.2 Treatment Groups

The treatment group refers are defined in Table **8**.

Table 8 **Treatment Groups**

Treatment	**Definition**
ARGX-117 Dose Regimen 1 [redacted]	[redacted]
ARGX-117 Dose Regimen 2 [redacted]	[redacted]
ARGX-117 Dose Regimen 3 [redacted]	[redacted]
Placebo Cohort 1 (PBO C1)	Placebo received in cohort 1
Placebo Cohort 2 (PBO C2)	Placebo received in cohort 2
Total Placebo (Total PBO)	Placebo received in cohort 1 or 2

For the first interim analysis, 2 treatment groups will be displayed: ARGX-117 dose regimen 1 and Cohort 1 in the summary tables, figures and listings. For the second interim and final analysis, the following treatment groups will be presented depending on the decision of the EDRT:

- ARGX-117 Dose Regimen 1, ARGX-117 Dose Regimen 2 (option 1) and Placebo or,
- ARGX-117 Dose Regimen 1, ARGX-117 Dose Regimen 3 (option 2) and Placebo or,
- ARGX-117 Dose Regimen 1, ARGX-117 Dose Regimen 2 (option 3), ARGX-117 Dose Regimen 3 (option 3) and Placebo; [redacted] placebo groups will be combined for all analyses and not presented separately.

6.2.3 Definition of Baseline

IVMP baseline: The last available and first non missing value collected before or on Day 1 IVMP. Assessments performed at Day 1 IVMP but without time information collected will be considered eligible to the IVMP baseline. In the case there are 2 assessments performed at Day 1 IVMP, and the time is missing for one of them, the assessment with time information collected will be assigned to IVMP baseline.
In addition, for HRPQ questionnaire, the questionnaire with at least one non missing item based on SDTM datasets for at least one item from HRPQ01 to HRPQ09 will be used for IVMP baseline.

DBTP baseline (baseline): The last available and non missing value collected before the first administration of IMP will be used as baseline. Assessments performed on the same day as the first IMP administration but without time information collected or with time information exactly equal to the time of first IMP administration and which are planned predose will be considered as predose. For pharmacodynamic assessments, assessments performed on the same day as the first IMP administration but without time information and which are planned predose will be considered as predose. Efficacy assessments (including questionnaires, grip strength, mMRC and 9-HPT) completed post administration on the day of the first administration of IMP will be considered in the baseline selection in the absence of pre administration assessments from that day.
In addition, for HRPQ questionnaire, the questionnaire date with at least one non missing item based on SDTM datasets for at least one item from HRPQ01 to HRP09 will be used for IVMP baseline.If not otherwise specified, the term baseline will be used to refer to DBTP baseline.

6.2.4 Adjustments for Covariates

[redacted] as recorded per CRF will be used, rather than the values coming from the IRT system.

For continuous variables, baseline values and IVIg dose frequency will be explored in the statistical modeling.

6.2.5 Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made.

6.2.6 Subgroups

6.2.6.1 Subgroup category for secondary endpoints

For the secondary endpoints derived from mMRC, Grip strength, MMN-RODS© and 9-HPT , descriptive statistics will be presented per subgroup based on the [redacted]. The value as entered into the CRF will be used, and not the value from IRT, should these defer.

6.2.6.2 Subgroup categories for Demographics

Table 9 Subgroup categories for Demographics

Subgroup	Categories
Sex	Male, Female
Age	• 18 to <65 years • ≥65 years
Weight	• <50 kg • 50 to <75 kg • 75 to <120 kg • ≥120 kg
BMI	• Underweight: <18.5 kg/m^2 • Normal weight: 18.5 to <25 kg/m^2 • Overweight: 25 to <30 kg/m^2 • Obese: ≥30 kg/m^2
Region	• North America: US, Canada • Europe: EU/EEA/EFTA/UK • Asia • Rest of World

6.2.7 Missing, Unused, and Spurious Data

6.2.7.1 Adverse events missing dates

AEs will be considered treatment-emergent based on their start date/time.

Imputation of missing/partial AE dates/time will be performed only to identify treatment-emergent AEs. If the AE start date/time is incomplete or missing, the AE will be considered treatment-emergent unless the available part of the AE start or stop date/time provide evidence that the event did not occur following initiation of IMP. The following rules allow for an imputed start and stop date that adheres to this convention:
For partial or missing AE start date/time the following imputation will be applied:

1. If year is not missing and is after the year of first IMP dose:
    a. If month is missing, then month will be imputed as January.
    b. If day is missing, then day will be imputed as the first of the month.

2. If year is not missing and is the same as the year of the first IMP dose:
    a. If month is missing, then impute the month as the month of the first dose date.
    b. If day is missing, and the month is the same as the month of the first dose date, then impute day as the day of the first dose date.
    c. If day is missing but month is after the month of first dose date, then impute day as the first day of the month.

3. If year is missing then impute the date of the first IMP administration.
4. If the start date is completely missing, but the AE is either ongoing or the stop date or imputed stop date (in case of partially missing stop date) is after the first dose date then impute the start date as the first dose date.

5. For any cases involving the rules above, if the AE stop date or imputed stop date (in case of partially missing stop date) is before the AE start date, then do not impute the AE start date and assume that the AE is treatment-emergent for the purpose of the analysis. Further, if the AE stop date or imputed AE stop date (in case of partially missing stop date) occurs prior to the first dose date, do not impute the AE start date, and assume that the AE is not treatment-emergent.

For partial or missing AE start time the following imputation will be applied:
1. If date or imputed date is the date of the of the first IMP dose, then the time will be the time of the IMP administration
2. If date or imputed date is different from the date of the of the first IMP dose, then time will be 00 h 00 min.

For partial and missing AE stop date/time the following imputation will be applied:

1. If Day only is missing, incomplete stop dates will be replaced by the last day of the month, if not resulting in a date later than the date of the participant's death or date of study discontinuation. In the latter case, the date of death/date of study discontinuation will be used to impute the incomplete end date.
2. If Day & Month are missing, Day & Month will be replaced by 31DEC, if not resulting in a date later than the date of the participant's death or date of study discontinuation. In the latter case, the date of death/ date of study discontinuation will be used to impute the incomplete end date.
3. In all other cases the incomplete end date will not be imputed.

If time is missing, the time will be imputed to 23:59.

Imputed dates and times will not be listed nor will day of onset or event durations be presented if the required date(s) is imputed.

6.2.7.2 Prior and concomitant medications missing dates

Medications and procedures administered will be classified by period of use as prior, concomitant or both prior and concomitant to IMP therapy. In the event of partial dates, the available date information will be used to categorize the initiation period accordingly. In the event that the classification is ambiguous, including for cases of completely missing dates, the medication will be assumed to be both prior and concomitant unless indicated as prior only due to the given stop date.

The following date imputation rules for partially missing dates reflect the above convention:

1. End date: Missing day will be imputed as the last day of the month, and missing month will be imputed by December, if not resulting in a date later than the date of the participant's death, date of study discontinuation or date of study completion. In the latter case, the date of death/date of study discontinuation/ date of study completion will be used to impute the incomplete end date.
2. Start date: Missing day will be imputed as the first day of the month, and missing month will be imputed by January.
3. If the start date is completely missing, then:

a. If the end date is prior to the date of first administration of the IMP, then the medication is considered as prior
b. If the end date is prior to the date of last administration of the IMP, then the medication is considered as prior and concomitant
c. If the end date is completely missing or after the date of last administration of the IMP, then the medication is considered as prior and concomitant.

6.3 Study Population

6.3.1 Participant Disposition

Summary data for the ENR set will be presented overall. The denominator for all percentages will be the total number of enrolled participants. Summary data for the SAF set will be presented for each cohort by treatment group and overall.

A tabulation of participant disposition will be presented by treatment group and overall, for enrolled participants, including:

- Number of screened participants
- Number of participants who entered, discontinued the IVDP (including completed IVDP but did not enter IVMP), and who completed IVDP and entered IVMP

- Number of participants who entered, completed and discontinued the IVMP
- Number of screen failures during the screening period, IDVP and IMVP along with the reasons. Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the DBTP. A participant can be screening failure if the participant did not meet protocol criteria at screening visit, IVM1 or V1 or discontinued the study before randomization
- Number of participants randomized

A tabulation of participant disposition will be presented for each cohort by treatment group and overall, for SAF set, including:

- Number of participants who entered, discontinued the IVDP, and who completed IVDP and entered IVMP
- Number of participants randomized
- Number of participants randomized but not dosed
- Number of participants who completed DBTP, who are ongoing and who early discontinued treatment or DBTP and associated reasons for discontinuation. Among these participants, the number of participants who entered into the subsequent periods (Safety follow period or LTE) or did not enter into the subsequent periods will also be described
- Number of participants entering into safety follow-up period, who completed safety follow-up period and who early discontinued the study and associated reason for discontinuation. Among these participants, the number of participants who completed or not the DBTP will be described
- Number of participants entering into the LTE

The number of participants in each analysis set will be also presented in the SAF set. The number of participants per country and site will also be provided using the SAF and ENR sets.

A summary of periods duration will be presented for each period for the SAF set (screening period, IVDP, IVMP, DBTP and Safety follow-up period). For IVDP, IVMP, DBTP and Safety follow-up period, IVIg frequency will be presented by IVIg frequency stratification factor.

The following by-participant listings will be presented.

- Study completion information, including the reason for premature study withdrawal
- Inclusion/exclusion criteria not met
- Inclusion in study Analysis Sets
- Allocation to treatment and IVIg dose frequency stratification factor

6.3.2 Demographic and Baseline Characteristics

Baseline, demographic, medical history, MMN disease history, IVIg history, will be summarized using descriptive statistics. Summary data for the SAF set will be presented for each cohort by treatment group and overall.

6.3.2.1 Demographics

Demographics will be summarized for the SAF sets.

Demographics and baseline data include age (years), sex, ethnicity, race, height (cm), weight (kg) and BMI (kg/m²). All data are collected at screening visit only except weight that is collected at screening and IMV3. BMI is auto calculated, defined as: Weight (kg)/(Height*Height) (m²).
Frequency tabulations will be provided for age category, sex, race, ethnicity, and region. Subgroup categories are defined in section 6.2.6.2. For race and ethnicity categories are per eCRF categories will be presented.

Demographic and baseline data will be provided in data listings.

6.3.2.2 Medical history

Medical history will be summarized for the SAF set.

Medical history (resolved and ongoing at screening) is summarized by participant incidence rates; therefore, a participant contributes only once to the count for a given medical history (SOC or preferred term).

Medical history will be reported in a listing.

6.3.2.3 MMN disease history and MMN diagnosis

MMN disease history will be summarized for the SAF set.

Estimated duration of the disease since diagnosis at randomization will be derived as follows:
Estimated duration of disease since diagnosis = (Date of randomization – date of diagnosis +1)/365.25.
For the date of diagnosis:

- if day and month are missing, 01-Jul will be imputed
- if day is missing, 15 will be imputed.

Estimated duration of the disease since diagnosis at randomization, the most affected hand and the 2 most important muscles groups affected by MMN will be reported.

For the estimated duration of the disease since diagnosis at randomization in the summary table, results will be rounded in year with no decimal places for min and max, one decimal place for mean median and 2 decimal places for SD.

A tabulation will summarize the confirmation of diagnosis and IVIg dependency at screening and IMV1 in the SAF set.
MMN history will be reported in a listing. Confirmation of diagnosis and IVIg dependency by MCC will be listed.

6.3.2.4 IVIg history

IVIg history will be summarized for the SAF set.

Time between historical first schedule of IVIg administration and screening will be derived as follows: Date of screening visit – start date of the first IVIg administration of IVIg +1

The start date of the first IVIg administration:
- if day and month are missing, 01-Jul will be imputed
- if day is missing, 15 will be imputed.

Time between first schedule of IVIg administration and screening will be summarized. For IVIg administration ongoing at screening, IVIg duration and dose and frequency will be summarized. IVIg frequency will be presented by stratification factor issued from the IWRS and eCRF if they differ.

IVIg duration ongoing at screening will be derived as follows:

screening date – starting date of last IVIg administration stable before screening *+ 1
* last IVIg administration stable before screening is defined as: for the IVIg administration ongoing at screening (ongoing = YES in IVIg history page with non-missing IVIg dose frequency), the oldest administration with same frequency and dose, independently of the treatment name.

The starting date of last IVIg administration stable before screening:
- if day and month are missing, 01-Jul will be imputed
- if day is missing, 15 will be imputed.

IVIg history will be summarized in a listing.

6.3.2.5 IVIg treatment during IVMP

For each participant, the average IVIg dose interval in weeks will be calculated as:

Average IVIg dose interval (weeks) = [(Starting date of the last IVIg administration during IVMP– starting date of the first IVIg treatment during IVMP)/ (Number of IVIg administrations during IVMP-1)]/ 7

Total IVIg dose (g/kg), average IVIg dose per week (g/kg) and average IVIg dose interval (week) will be summarized by treatment group and overall and by IVIg dose frequency subgroup using descriptive statistics during the IVMP on the SAF set.

During IVMP, for the total number of IVIg administrations, in case of unscheduled visits with IVIg administrations :
- If unscheduled visits are not on consecutive days, one unique IVIg administration should be counted per unscheduled visits
- If unscheduled visits are performed on consecutive days, then IVIg administrations performed on these consecutive day should be counted as a single administration.

In case of IVIg administrations given on several days for a single visit, a unique record (e.g. first day) should be considered to determine the dose of IVIg administered at this visit. The total IVIg dose over the IVMP period is the sum of the unique doses associated to each visit, including unscheduled visits.

All visits (scheduled, unscheduled) during IVMP will be taken into account.

IVIg administrations during IVDP and IVMP will be listed.

6.3.3 Prior Medications and Procedures

Prior and concomitant medications will be coded using the WHO Drug dictionary.

Prior and concomitant medications and procedures will be summarized for the SAF set. Results for prior medications will be presented for each treatment group and overall, by Anatomic Therapeutic Class (ATC) level term 1, ATC level 3 and generic term.

Prior medications will be defined as any medication with a start date/time before the date/time of first dose of IMP. Refer to section 6.2.7.2 for partial or missing date rules).
If the end date is after the end of study date, end date will be imputed to end of study date.

Prior concomitant procedures will also be summarized and provided in a listing.

6.3.4 Concomitant Medications and Procedures

All concomitant evaluations will be summarized for the SAF set during the DBTP.

Medications (or procedure) with a start date/time on or after the date/time of first dose of IMP will be considered concomitant. Medications (or procedures) taken prior to the first dose of IMP and continuing after the first dose of IMP will be considered both prior and concomitant. All medications starting or ongoing during the DBTP are concomitant to this period. All medications starting or ongoing during the SFU period are concomitant to this period.

If a medication (or procedure) date is missing, or partially missing, and it cannot be determined whether it was taken on or after start of treatment, it will be considered a concomitant medication (or procedure). Refer to section 6.2.7.2 for partial or missing date rules).

If the end date is after the end of study date, end date will be imputed to end of study date.

Results for concomitant medications will be tabulated by ATC level 1, ATC level 3 and generic term for the DBTP period.

The use of concomitant medications and procedures will be included in by-participant data listing.

6.3.5 Exposure and Compliance

Exposure and compliance of ARGX-117 and Placebo will be summarized in SAF set for each cohort.

Summary statistics of duration of treatment (weeks), number of infusions, duration for the first infusion (min), dose for the first infusion (mg/kg), average duration for subsequent infusions (min), average dose for the subsequent infusions (mg/kg) and cumulative dose (mg/kg) will be presented.

Duration of treatment (days) will be defined as (Last Dose Date – Start Dose Date + 1)/7.
Dose (mg) is calculated as volume of IMP (collected in CRF) multiplied by strength [redacted]). Dose (mg/kg) is calculated by dose divided by weight in kg at baseline.

For cohort 2, in the case of selection of dose regimen 3, for participants who received active treatment, administrations of placebo will be taken into account in the calculation of the dose related parameters (number of infusions, average duration for subsequent infusions, average dose for the subsequent infusions and cumulative dose)

Compliance will be derived as follows:

$$Compliance\ (\%) = \frac{Number\ of\ doses\ received}{Number\ of\ expected\ doses} \times 100$$

Where the number of doses expected is the number of planned doses up to v14 (D113) or early treatment discontinuation visit (if a participant withdraws during the DBTP). In practice, all possible planned visits, including the potentially missed visits, up to the last planned visit in the DBTP of the participant available in the database, will be used as the denominator.

IMP exposure and compliance will be listed.

6.3.6 Summary of Baseline efficacy endpoints

A summary of baseline efficacy endpoints will be displayed for mMRC-10 sum score, mMRC-14 sum score, GS-daily average for the most affected hand and the less affect hand, GS 3 day moving average for the most affected hand and the less affected hand, MMN-RODS centile metric score, CAP-PRI total score and average FSS score.

6.4 Safety Evaluations

6.4.1 Adverse Events

All adverse events evaluations will be performed in the SAF set. For the DBTP period, TEAEs will be presented up V14 for participants who roll over to the LTE and for other participants through to the day before the first visit in the safety follow-up period (FUV1) or the date of last available data if FUV1 has not been attended.

AE onset and duration will be derived as follows:

- AE onset date (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 date will be computed only if the AE start date is fully known.

- AE duration (days)=
  - AE end date – AE start date +1
  - Study discontinuation date – AE start date + 1 day (when the AE is not resolved at the end of the study). In this case, the duration will be presented as ">x days"

  AE duration will be computed only if the start and end date are fully known.

- AE rate per 100 patients' year of follow-up (PYFU) defined as 100 * the number of events divided by the sum of the follow-up time during which an event is considered treatment-emergent of all participants per treatment arm expressed in years (ie, divided by 365.25) during the period. AE rate will be derived for DBTP and DBTP and safety follow-up combined as defined in section 5.2.

The following definitions will be used for the analysis of adverse events (AEs):

Table 10 Adverse Event Definitions

	Definition
Treatment-emergent adverse event (TEAE)	Treatment-emergent AEs are defined as AEs with onset on or after the first administration of IMP
Treatment Related AE	Any AE reported by the investigator as treatment related (ie, "Relationship to ARGX-117/Placebo= Related" in the CRF "Adverse event" page) and those of missing relationship.
IVIg Related AE	Any AE reported by the investigator as IVIg related (ie, "Relationship to IVIg treatment= Related" in the CRF "Adverse event" page) and those of missing relationship.
Procedure Related AE	Any AE reported by the investigator as procedure related (ie, "Relationship to any study procedure = Related") and those of /missing relationship.
Serious Adverse Events (SAEs)	Any AE with "Is this a serious adverse event?" = Yes in the CRF "Adverse event" page.
Non serious Adverse Events	Any AE with "Is this a serious adverse event?" = No in the CRF "Adverse event" page.
Adverse Events Leading to Interruption of IMP	Any AE with "ARGX-117/Placebo interrupted?" = Yes in the CRF "Adverse event" page.
Adverse Events Leading to Permanent Treatment Discontinuation	Any AE with "ARGX-117/Placebo withdrawn" = Yes in the CRF "Adverse event" page.
Adverse Events Leading to Death	Any AE with fatal outcome or AE with NCI CTCAE grade = 5
Adverse Event of Special Interest	AESIs are defined as events with grade ≥ 3 and a PT that falls under the MedDRA SOC Infections and infestations.
Adverse Event of Hypersensitivity Reactions	Any AE with PT from SMQ (narrow) selection for hypersensitivity reaction
Adverse events of Anaphylactic Reaction	Any AE with PT from SMQ (narrow) selection for anaphylactic reaction
Adverse Events of Local Reactions	Any AE with MedDRA PT in the MedDRA High Level Group Term of administration site reactions, regardless of time of onset.

Summary tables of TEAEs will be presented for the DBTP (SAF set).

AE will also be allocated to the first period that is possible based on the available part of the AE start and stop date/time If, for a participant not entering the safety follow-up period or LTE, an AE occurs following V14 or treatment discontinuation, then the AE will be counted in the DBTP.

Overview Tables of TEAE
Overview summary tables will be presented by treatment group for the DBTP. The number and percentage of participants who had at least 1 TEAE and the event rate per 100 PYFU in each of the following categories will be displayed during the DBTP in the SAF set:
- Treatment-emergent adverse event (TEAE)
- IMP Related TEAE
- IVIg Related TEAE
- Procedure Related TEAE
- treatment-emergent SAE
- Serious IMP related TEAE
- TEAEs for which IMP was interrupted
- TEAE Leading to Withdrawal of IMP
- TEAE leading to Death
- TEAE with CTCAE grade ≥ 3
- treatment-emergent AESI
- TEAE of hypersensitivity reactions
- TEAE of anaphylactic reactions
- TEAE of local reactions

[redacted]

[redacted]

Additionally, an overview table of TEAEs will be displayed during the DBTP and SAFFU periods combined in the SAF set.

In these tabulations, each participant will contribute only once (ie, via the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes that occurred.

Summary Tables of AE by SOC and PT
Summary tables will be presented by treatment group. The selected TEAEs listed above, excluding fatal events and those leading to interruption of IMP, will also be summarized in terms of participant incidence rates and number of events by SOC and PT during the DBTP in the SAF set.

A summary table of TEAE by SOC and PT will be provided for during the DBTP and SAFFU periods combined in the SAF set. Note that in any tabulation, a participant will contribute only once to the count for a given adverse event (SOC or Preferred Term), regardless of the number of episodes that occurred.

All AEs will be listed, including pretreatment AEs.
The following by-participant listings will be presented in the SAF set:

- all adverse events
- treatment-emergent SAE
- TEAE leading to withdrawal of IMP
- TEAE Leading to Interruption of IMP
- treatment-emergent AESI
- TEAE leading to death

6.4.2 Laboratory Data

The list of parameters to be measured (biochemical, hematological, coagulation and urine), systemic lupus erythematosus (SLE) is provided in the following table. Clinical laboratory values will be expressed using conventional SI units for the analysis as defined by the SDTM Controlled Terminology.

Table 11 Clinical Laboratory Tests and SI units

Blood Chemistry (serum) (SI unit):	
Blood urea nitrogen (BUN) (mMol/L)	Calcium (mmol/L)
Glucose (random) (mmol/L)	eGFR (mL/min/1.73m^2)
Glucose (fasting)	AST (U/L)
Creatinine (umol/L)	ALT (U/L)
Creatine kinase (U/L)	ALP (U/L)
Creatinine Kinase-MB (ug/L)	Total protein (g/L)
Total IgG (umol/L)	Total bilirubin (umol/L)
Potassium (mmol/L)	Direct bilirubin (umol/L)
Sodium (mmol/L)	c-reactive protein (mg/L)
Hematology (SI unit):	
Red blood cells (x 10^{12}/L)	Reticulocytes/Erythrocytes (%)
Platelets (x10^9/L)	Reticulocytes (10^9/L)

Hemoglobin (g/L)	Neutrophils (x10^9/L) Neutrophils/Leukocytes (%)
Hematocrit (packed cell volume [PVC]) (%)	Eosinophils (x10^9/L) Eosinophils /Leukocytes (%)
Mean cell volume (MCV) (fL)	Lymphocytes (x10^9/L) Lymphocytes/Leukocytes (%)
Mean cell hemoglobin (MCH) (pg)	Basophils (x10^9/L) Basophils /Leukocytes (%)
White blood cells (10^9/L)	Monocytes (x10^9/L) Monocytes/Leukocytes (%)
Coagulation	
International normalized ratio	
Urinalysis	
pH	Nitrite
Specific gravity	Leukocyte esterase
Glucose	White blood cells
Protein	Crystals
Blood	Casts
Ketones	Epithelial cells
Bilirubin	Yeast cells
Urobilinogen	
Pregnancy test	
Pregnancy test	FSH (IU/L)
SLE panel	
ANA	If the SLE panel detects ANA, additional autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2- glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) will be evaluated.

All clinical laboratory parameters will be summarized in the SAF set on the DBTP and the safety follow-up period.

In the event of repeat values, the last non missing value per visit will be used. In the case of a protocol specified laboratory result being of the form "<x", to include in continuous summaries, the numeric result will be derived as x. For results reported as ">x", the numeric result will be derived as x.

For each quantitative laboratory parameter (chemistry, hematology, coagulation and urinalysis), the actual value and change from baseline at each visit/time point on DBTP will be summarized by treatment group using descriptive statistics.

All laboratory data will be listed, but only for participants with any postbaseline abnormality or toxicity grade ≥1.

For laboratory parameters with no toxicity grades results will be categorized according to reference ranges from the central laboratory using non imputed value and limits as:

Low if parameter result is < Lower Limit of Normal (LLN)

High if parameter result is > Upper Limit of Normal (ULN)

Normal if parameter value is within normal range (LLN ≤ result ≤ ULN)

Treatment-emergent out-of-range values are defined as laboratory values:
- with normal values at baseline and low or high value at any post baseline visit, or
- with low values at baseline and high at any post baseline visit, or
- with high values at baseline and low at any post baseline visit.

If baseline is missing, any post-baseline abnormality will be considered treatment emergent.

For parameters with toxicity grades (Table 12), Treatment-emergent toxicity grade values are defined as laboratory values with higher grade post-baseline compared to the grade at baseline. If baseline is missing any postbaseline toxicity will be considered treatment-emergent.

The CTCAE Version 5.0 will be used as the basis for toxicity grading. CTCAE grades will be programmatically derived as described in the Table 12 when applicable.

Table 12 Toxicity Grading for Selected Laboratory Tests

Paramater	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alanine amino transferase (ALT)		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Alkaline phosphatase (ALP)		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Aspartate amino transferase (AST)		>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
Creatine kinase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN

Paramater	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-6.0 *ULN	>6.0 *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
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
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

If grade is different from grade 1 to 4, grade will be assigned to 0.

For non gradable parameters per NCI CTCAE grading system, shift tables will be created to summarize the number and proportion of participants with shifts from baseline category to post baseline category ("Low"; "Normal", "High", treatment-emergent out-of-range) by treatment group and visit. Shift tables from baseline to worst postbaseline category will also be presented. In case of low and high post-baseline values, a category 'low + high' will be defined.

For laboratory parameters which can be graded per NCI CTCAE grading system, the information will be summarized using a shift table summarizing the baseline NCI CTCAE grade (0,1,2,3,4) versus post baseline category NCI CTCAE grade by treatment group and visit. Shift tables from baseline to worst post DBTP baseline NCI CTCAE grade will also be displayed. If there is no evaluation, the worst grade will be set to 'Missing'. Parameters with toxicity grades defined in both directions (decreased and increased) will be shown by direction. Numbers and cumulative numbers over decreasing toxicities grading of participants with treatment-emergent toxicities will also be shown.

All laboratory data will be listed, but only for participants with post baseline abnormalities or toxicity grade ≥ 1.

For ANA titers (SLE panel) , the number and percentage of participants will be summarized by category at each visit in SAF set on DBTP. The following categories for ANA titers will be defined:

- Negative, in case of negative result
- Positive:
  - [redacted]

In case of multiple titers results for the same assessment, the worst assessment (ie most positive) should be considered.

Shift tables from baseline to worst post baseline category ("Negative", " Low positive" and "High positive") will also be presented.

A listing of participants with ANA titer > 1:80 will be provided and will include the following assessments: anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2- glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP.

A listing of Laboratory results for participants entering into the SFU period will be provided.

6.4.3 Vital Signs

Vital signs parameters include:

- Temperature (°C)
- Systolic blood pressure (SBP supine position) (mmHg)
- Diastolic blood pressure (DBP supine position) (mmHg)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)

The "Low", "Normal" and "High" ranges for each vital signs (except heart rate) will be derived as described in Table 13:

Table 13 Low, Normal and High Ranges for Vital Signs (Temperature, SBP, DBP and Respiratory Rate)

Parameters	Range		
	Low	Normal	High
Temperature (°C)	< 35.8	35.8 -37.5	> 37.5
SBP (mmHg)	< 90	90 -150	>150
DBP (mmHg)	< 45	45 – 90	> 90
Respiratory rate	< 12	12 – 25	> 25

Actual value and change from baseline will be summarized for each parameter and visit by treatment group and overall using descriptive statistics in the SAF set on DBTP period.

Treatment-emergent out-of-range values are defined as follows:
- with normal values at baseline and low or high value at any post baseline visit, or
- with low values at baseline and high at any post baseline visit, or
- with high values at baseline and low at any post baseline visit.

If baseline is missing any postbaseline abnormality will be considered treatment-emergent.

Shift tables will be created to summarize the number and proportion of participants with shifts from baseline to all visits according to the normal range “Low”, “Normal”, “High” and “Treatment-emergent” by treatment group and visit. The worst post DBTP baseline will also be presented. In case of low and high post- baseline values, a category ‘low + high’ will be defined. Numbers of participants with treatment-emergent abnormalities will also be shown.

All vital signs data will be listed for participants with post- baseline abnormalities.

6.4.4 Electrocardiogram

Triplicate 12-lead ECGs are performed at screening and V1 visit and single 12-lead EGG for the other visits. For the other visits, a single 12-lead ECG is performed. Mean values of the triplicates will be calculated per time point and rounded to 1 decimal. Throughout the analysis, including the derivation of baseline and abnormalities, the mean values will be used in case the assessment was performed in triplicates. Individual triplicate values will only be listed.

ECG parameters include heart rate, PR, QRS, QT, QTcB and QTcF intervals.

The “Low”, “Normal” and “High” ranges will be derived for heart rate, PR and QRS as described in Table 14.

Table 14 Low, Normal and High Ranges for ECG parameters (Heart rate, PR and QRS)

Parameters	Range		
	Low	Normal	High
Heart rate (beats/min)	< 40	40 -100	> 100
PR (ms)	< 120	120 – 220	> 220
QRS (ms)	< NA	0-120	> 120

NA: Not Applicable

Treatment-emergent out-of-range values are defined as follows: :
- with normal values at baseline and low or high value at any post baseline visit, or
- with low values at baseline and high at any post baseline visit, or
- with high values at baseline and low at any post baseline visit.

If baseline is missing any postbaseline abnormality will be considered treatment-emergent.

For QTcB and QTcF (ms), the following categories will be derived:
- For the actual values: ≤ 450 (normal),]450 ;480],]480 ; 500], and > 500
- For the change from baseline:≤ 30 (normal),]30;60] and > 60.

For QTcB and QTcF, a treatment-emergent abnormality is defined as any postbaseline abnormality which was not present at baseline or which worsened following baseline (eg, QTcF]450; 480] ms at baseline and>500 ms postbaseline). If baseline is missing any postbaseline abnormality will be considered treatment-emergent.

ECG parameters (heart rate, PR, QRS, QT, QTcB and QTcF intervals) will be summarized using actual value and change from baseline at each visit/time point by treatment group and overall in the SAF set on the DBTP.

For heart rate, PR and QRS, shift tables will also be created to summarize the number and proportion of participants with shifts from baseline category to “Low”, ”Normal”, “High”, treatment-emergent by treatment group and visit . Shift tables from baseline to worst post DBTP baseline category will also be presented. In case of low and high post- baseline values, a category ‘low + high’ will be defined.

All ECG data for participants with post baseline abnormalities will be listed.

For QTc, shift tables will be created to summarize the number and proportion of participants with shifts from baseline to all visits according to the abnormality by treatment group and visit. Shift tables from baseline to worst post DBTP baseline abnormality will also be presented. Numbers and cumulative numbers of participants with treatment-emergent abnormalities will also be shown.

Abnormalities of QTc changes will be summarized at each post-baseline analysis visit and at the worst-post-Baseline analysis visit. Number and Cumulative numbers of participants with change abnormalities will also be shown.

6.4.5 Suicidal Behavior

All suicidal behavior evaluations will be performed in SAF set.

Suicidality assessments are conducted by specifically answering the following question, derived from the Patient Health Questionnaire (PHQ-9) depression questionnaire:
"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 answers with the associated scores are:
- "Not at all [0]",
- "Several days [1]",
- "More than half the days [2]",
- "Nearly every day [3]".

Number and percentage of participants for each answer will be summarized at each visit during DBTP in the SAF set. The worst DBTP post baseline suicidal ideation during DBTP will also be reported.

All PHQ-9 assessments will be listed, but only for participants with a post baseline PHQ-9 answer not equal to 'Not at all'.

6.5 Efficacy Evaluation

6.5.1 Efficacy of ARGX-117 compared to placebo on muscle strength and/or motor function in adult participants previously stabilized with IVIg

6.5.1.1 Retreatment with IVIg

Summary data will be presented by treatment group. This analysis will be performed in the SAF set only.

- Time to the first retreatment with IVIg since the final IVIg treatment of the IVMP

Time to first retreatment with IVIg is defined as the time from last IVIg administration before randomization (including unscheduled visits) up to the first IVIg retreatment during DBTP.

Time to first retreatment with IVIg = (start date of first IVIg retreatment during DBTP – stop date of last IVIg treatment before randomization)

For participants who are not retreated with IVIg during the DBTP this will be calculated as:

Time to first retreatment with IVIg = censoring date – stop date of last IVIg treatment before randomization

If the stop date of last IVIg treatment before randomization is missing then the start date will be used.

The censoring date will be determined as follows:

- If the participant completes DBTP, the censoring date will be the date of last visit V14 (D113)
- If the participant early discontinues treatment, the censoring date will be the date of early discontinuation of treatment
- If the participant is ongoing in cohort 2, the censoring date will be the date of the data cutoff date

Participants who are lost to follow-up in the DBTP will be censored at the date of last visit available.

Time-to-event variables will be descriptively presented with median times, quantiles, and number and percentage of participants censored and with event (KM estimates). The probability of participants being retreated will be displayed by treatment group in the form of cumulative probability curves estimated using the non parametric Kaplan-Meier method. The CI for the median will be calculated using the Brookmeyer and Crowley method. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Time to IVIg retreatment will be listed.

- Time to relapse

Time to relapse is defined as the time from randomization up to the time participant meets threshold for clinical deterioration.
For a participant, the threshold for relapse status is met if one of these criteria is established:
[redacted]

Time to relapse = (date of first clinical deterioration during DBTP – date of randomization) + 1

The data of participants who do not meet criteria for clinical deterioration will be censored. The censoring date will be determined as follows:

- If the participant completes DBTP, the censoring date will be the date of last visit V14 (D113)
- If the participant early discontinues treatment during DBTP, without clinical deterioration, the censoring date will be the date of early discontinuation of treatment
- If the participant is ongoing in cohort 2, the censoring date will be the date of the data cutoff date

Participants who are lost to follow-up in the DBTP will be censored at the date of last visit available.

The statistical analysis will be similar to the survival analysis described above for time to first retreatment with IVIg.

Time to relapse data will be listed.

- Number of participants retreated with IVIg

The number and percentage of participants retreated with IVIg during the DBTP will be summarized by treatment. Categories will be presented as follows:

- Not retreated
- Retreated once
- Retreated twice
- Retreated more than twice
- Total number of IVIg administrations

In addition, a cross tabulation will display the status of IVIg retreatment (Yes/ No) according to the following worsening status:

- clinical deterioration [redacted]

An additional table with each worsening status combined with the IVIg retreated status (IVIG retreated / Not retreated with IVIg) will be summarized as well.

- IVIg administrations during DBTP

The following endpoints will be described for participants retreated with IVIg: Number of IVIg administrations during DBTP, Total IVIg dose (g/kg), Average IVIg dose / week (g/kg) and Average IVIg dose interval (weeks)

During the DBTP, IVIg administrations reported on several visits and linked to the same visit number should be counted as a single administration. In case of IVIg administrations performed on several days for unscheduled visits, and within maximum 5 days apart from the first one to the latest one, then it should be counted as a single administration. The total number of IVIg retreatments is the sum of single IVIg administrations during DBTP. The total IVIg dose over the treatment period is the sum of doses over all single IVIg administrations.

- Number of IVIg administrations during DBTP

The number of IVIg retreatments during the DBTP will be presented.

- Total IVIg dose (g/kg)

The total IVIg dose (g/kg) during the DBTP will be presented by IVIg dose frequency subgroup.

- Average IVIg dose / week (g/kg)

The average IVIg dose per week (g/kg) during the DBTP will be presented by IVIg dose frequency subgroup.

Average IVIg dose per week (g/kg)= Total IVIg dose / [(End DBTP date – starting date of the first IVIg retreatment+1)/7]

- Average IVIg dose interval (weeks)

For each participant, the IVIg interval in weeks between 2 retreatments will be calculated as:

Average IVIg dose interval (weeks) = [(Starting date of the nth IVIg retreatment – starting date of the first IVIg retreatment)/ (Number of IVIg administration during DBTP-1)]/ 7

The average IVIg dose interval in weeks for participants retreated at least twice during the DBTP will be presented by IVIg dose frequency subgroup.

The number of IVIg administrations during DBTP, the total IVIg dose, the average IVIg dose pr week and the average IVIg dose interval will be listed.

6.5.1.2 Modified Medical Research Council (mMRC)

The mMRC sum scores evaluate motor strength/weakness from predetermined muscle groups (upper and lower limbs). Each muscle group is scored from 0 (paralysis) to 5 (normal strength). The total score is based on the sum of both the left and right side of the body. The mMRC-10 Sum Score assesses 10 groups of muscles yielding to a total score from 0 to 100 and the mMRC-14 Sum Score assess 14 groups of muscles yielding to a total score from 0 to 140 (Table 15).

Table 15 Muscle Groups Tested for Each mMRC Sum Score

Muscle Groups Tested on Both Sides	mMRC 10-Sum Score	mMRC 14-Sum Score
Upper limbs		
Shoulder abductors	X	X
Elbow flexors	X	X
Elbow extensors	X	X
Wrist extensors	X	X
Wrist flexors	X	X
Finger flexors		X
Finger extensors at metacarpophalangeal joints		X

Muscle Groups Tested on Both Sides	mMRC 10-Sum Score	mMRC 14-Sum Score
Thumb abductor		X
Index finger abductor		X
Lower limbs		
Hip flexors	X	X
Knee flexors	X	X
Knee extensors	X	X
Foot dorsal flexors	X	X
Foot plantar flexors	X	X
Total score[a]	0-100	0-140

mMRC sum score analyses will be performed in SAF set. Analysis will be performed as defined in 6.2.1.2.

mMRC-10 sum score

mMRC-10 sum score and baseline mMRC-10 sum score will be re-derived and used for the analysis (refer to section 6.2.1.1). If any muscle score is missing, the mMRC-10 sum score will be set to missing.

- Value and Change from baseline in mMRC-10 sum score

On the IVMP, actual value and change from IVMP baseline of mMRC-10 sum score will be summarized for each visit.

On the DBTP, actual value and change from baseline of mMRC-10 sum score will be summarized for each visit (as defined in 6.2.1.2).

[redacted]

[redacted]

- Net iAUC per week of the change from baseline in mMRC-10 sum score

Net iAUC of the change from baseline in mMRC-10 sum score is defined as the total area under the curve which is above 0 (ie, positive) minus the area below 0. It will be derived using a linear trapezoidal rule.

Net iAUC $_{last\ assessment}$ per Week

Net iAUC $_{last\ assessment}$ per week =[(iAUC$_{v1\text{-}v3}$ + iAUC$_{v3\text{-}v4}$ +…+ iAUC$_{vn\text{-}1\text{-}vn}$)/ ((date of last analysis visit during DBTP – date of baseline + 1)/7)], where n is the last analysis visit number of mMRC-10 assessment with available data.

The calculation of net iAUC $_{last\ assessment}$ per week is detailed in appendix 9.4.

If net iAUC is positive [resp. negative] it would imply that there is an improvement [resp. deterioration] on mMRC-10 sum score. If a score is missing at a post baseline visit, the iAUC will be calculated from the last non missing available assessment up to the next non missing assessment.

Net iAUC per week will be displayed by treatment group and overall using descriptive statistics.

Partial Net iAUC

Net iAUC$_{day1\text{-}week4}$, net iAUC$_{day1\text{-}week8,}$ net iAUC$_{day1\text{-}week12}$, and net iAUC$_{day1\text{-}week16}$ will be derived.

If the final landmark time point is missing (week 4, week 8, week 12 and week 16 for net iAUC$_{day1\text{-}week4}$, net iAUC$_{day1\text{-}week8,}$ net iAUC$_{day1\text{-}week12}$, and net iAUC$_{day1\text{-}week16}$), the net iAUC will be considered missing. If an intermediate time point is missing the intermediate data point will be considered as missing, the partial net iAUC will be calculated from the last non missing available assessment up to the next non missing assessment within the interval.

Net iAUC$_{day1\text{-}week4}$, net iAUC$_{day1\text{-}week8,}$ net iAUC$_{day1\text{-}week12}$, and net iAUC$_{day1\text{-}week16}$ will also be presented for participants who have an assessment of mMRC-10 sum score at week 4,week 8, week 12 or week 16, respectively.

- Proportion of participants showing a deterioration of at least 2 points as assessed by the mMRC-10 sum score

The number and percentage of participants showing a deterioration of at least 2 points in mMRC-10 sum score at last assessment during IVMP compared to IVMP baseline will be summarized.

On the DBTP, the number and percentage of participants showing a deterioration of at least 2 points in mMRC-10 sum score compared to baseline at last assessments derived visits (as defined in 6.2.1.2) will be summarized.

mMRC-10 Sum Score data will be listed.

mMRC-14 sum score

mMRC-14 sum score will be re-derived and used for the analysis.

- Value and change from baseline in mMRC-14 sum score

On the IVMP, actual value and change from IVMP baseline of mMRC-14 sum score will be computed for each visit.

On the DBTP, actual value and change from baseline of mMRC-14 sum score will be computed for each visit (as defined in 6.2.1.2).

[redacted]

- Value and change from baseline of the average of the mMRC-14 scores for the 2 most important muscle groups

For each visit, the mMRC-14 score for the 2 most important muscle groups will be averaged. If at least one value of one of the 2 most important muscle groups is missing, the average will be considered as missing.

On the IVMP, actual value and change from IVMP baseline of the average of the mMRC-14 score for the 2 most important muscle will be computed for each visit.

On the DBTP, the actual value and change from baseline of the average of the mMRC-14 score for the 2 most important muscle will be computed for each visit (as defined in 6.2.1.2).

mMRC-14 Sum Score data will be listed.

6.5.1.3 Grip strength (GS)

Hand GS measurements consist of 3 repeated contractions with the right hand followed by 3 repeated contractions with the left hand. GS are assessed on-site at trial visits and monitored daily.
These analyses will be performed in the SAF set.
The variables computed by eCOA and used for the analyses are in detailed in section 6.2.1.1 and appendix 9.3. Analysis will be performed as defined in 6.2.1.2.

GS Daily Average

The GS daily average will be derived for the most and less affected hand separately. If at least one value is missing for the most or less affected hand, the GS daily average will be considered as missing for the corresponding hand.

- Value, Change from baseline and percent change from baseline and maximal percent change of GS daily average

On the IVMP, actual value and change from IVMP baseline and percent change from baseline GS daily average will be summarized at last assessment for each hand (most affected and less affected).

On the DBTP, for each hand (most affected and less affected), the actual value and change from baseline and percent change from baseline GS daily average will be summarized at last assessments (as defined in 6.2.1.2).

For the computation of the percent change from baseline (either at IVMP baseline or DBTP baseline), in case of value of baseline equal to 0 for GS daily average, the value of baseline for the denominator will be imputed by 1.

[redacted]

- Net iAUC per week of the change from baseline of GS daily average

For each hand (most affected and less affected), net incremental AUC (net iAUC) of the change from baseline up to last assessment during DBTP will be derived using linear trapezoidal rule and standardized per week as follows:

Net iAUC $_{\text{last assessment}}$ per Week

Net iAUC $_{\text{last assessment}}$ per week=[(iAUC$_{\text{day1 -day2}}$+ iAUC$_{\text{day2-day3}}$+…+ iAUC$_{\text{dn-1,dayn}}$ /((date of last assessment – date of randomization + 1)/7)], where n is the day of the last assessment of GS daily average.

The calculation of net iAUC $_{\text{last assessment}}$ per week is detailed in appendix 9.4.

iAUC will be positive if there is an improvement of GS daily average measurements compared to baseline and negative otherwise. If a score is missing at a post baseline visit, the iAUC will be calculated from the last non missing available assessment up to the next non missing assessment.

Net iAUC per week will be displayed by treatment group and overall.

Partial Net iAUC

If there is a missing time point which is not a final landmark time point , the data point will be considered as missing, the net iAUC will be calculated from the last non missing available assessment up to the next non missing assessment.

For the final landmark time point (week 4 for net iAUCDay1-week4, week 8 for net iAUCDay1-week8, week 12 for net iAUCDay1-week12 or week 16 for net iAUCDay1-week16), the visit window will apply. If the final landmark time point is missing, the AUC will be considered as missing. Net iAUC$_{\text{day1- week4,}}$ net iAUC$_{\text{day1- week8,}}$ net iAUC$_{\text{day1- week12}}$ and net iAUC$_{\text{day1- week16}}$ will also be presented for participants who have an assessment of GS daily average at week 4, week 8, week 12 or week 16 respectively.

GS daily average data for IVMP baseline, last assessment during IVMP, baseline, last assessment during DBTP and last assessment before IVIg will be listed.
Participants who have a value below 8 Kpa at baseline will be excluded from the analysis.

GS 3 day moving average (day-2, day-1, day 0)

GS 3 day moving average will be derived for each hand (most affected and less affected). GS moving average will be derived from the third day after the first GS daily average assessment. In case of missing value of GS daily average, GS 3 day moving average will be calculated based on the number of non-missing GS daily average values.

- Value, Change from baseline, percent change from baseline of 3-day GS moving average

On the IVMP, the actual value and change from baseline and percent change from IVMP baseline GS 3-day moving average will be summarized at last assessment for each hand (most affected and less affected).

On the DBTP, for each hand (most affected and less affected), the actual value and change from baseline and percent change from baseline GS 3 day moving average will be summarized at last assessments (as defined in 6.2.1.2). For the computation of the percent change from baseline (either at IVMP baseline or DBTP baseline), in case of value of baseline equal to 0 for GS 3-day moving average, the value of baseline for the denominator will be imputed by 1.

[redacted]

- Proportion of participants with a decrease of more than 30% from baseline over 2 consecutive days of GS 3-day moving average

For each hand (most affected and less affected), the parameter will be derived.
The date of the decrease of more than 30% from baseline over 2 consecutive days will be set as the first of the 2 days consecutive reduction of GS 3-day moving average .

The proportion of participants with a GS 3 day moving average decrease of more than 30% from baseline over 2 consecutive days of GS 3-day moving average during the following period of time:
- Start of IMP and last non missing GS 3 day moving average assessment during DBTP
- Start of IMP and last non missing GS 3 day moving average assessment before IVIg retreatment
will be summarized by treatment group and overall using descriptive analysis.

GS 3-day moving average data for IVMP baseline, last assessment during IVMP, baseline, last assessment during DBTP and last assessment before IVIg will be listed.

Participants who have a value of 0 at baseline will be excluded from the analysis.

6.5.2 Functional Ability, Arm and Hand Function, Quality of Life, and Fatigue

MMN-RODS©

MMN-RODS© is a questionnaire to capture activity limitations specifically in participants with MMN. It consists of 25 items that are scored as follows: 0: Unable to perform, 1: Able to perform, but with difficulty and 2: Able to perform without difficulty.

MMN-RODS will be analyzed in the SAF set, using the centile metric.

The total raw score will be calculated by summing the raw score of each item (range 0-50). If at least one item has a missing value, the total raw score will be considered as missing.

The total raw score will be transformed into a centile metric score as described in appendix 9.5. The centile metric score ranges from 0 (most severe activity and social participations limitations) to 100 (no activity and no social participation limitations).

On the IVMP, actual values and change from baseline of MMN-RODS score, using the total raw score and the centile metric will be summarized by visit.

On the DBTP, actual values and change from baseline of MMN-RODS score, using the total raw score and the centile metric will be summarized by visit (as defined in 6.2.1.2).

9-HPT

Analyses will be performed in the SAF set.

The 9-HPT is a quantitative test of upper extremity function. Two trials are performed for each hand (the dominant and non dominant hand). The total time to complete each trial in seconds is recorded in eCOA.

For each assessment, the 2 trials for each hand will be averaged. If at least one value is missing for the dominant or non dominant hand, the average value for the corresponding hand will be considered as missing In case, the total time for a trial exceeds 300 seconds, this trial will be excluded from the analysis, including the baseline values.
On IVMP, actual value, change from IVMP baseline and percent change from IVMP baseline of 9-HPT average time will be summarized by visit for each hand on IMVP period.

On the DBTP, actual value and change from baseline 9-HPT and percent change from DBTP baseline of average time will be summarized by visit (as defined in 6.2.1.2) for each hand.

9-HPT data will be listed.

EQ-5D-5L

These analyses will be performed in SAF set.

The EuroQol 5-dimension questionnaire (EQ-5D-5L) consists of 2 parts:

- A descriptive system of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels of response ranging from 1 (no problem) to 5 (extreme, unable to do so)
- A 20-cm vertical visual analog scale (VAS) with endpoints 0 (the worst health you can imagine) and 100 (the best health you can imagine).

For the last assessment analysis visit during DBTP and last assessment before first IVIg retreatment analysis visits, categories of improvement will be classified as follow:

- No change: the score is equal to baseline
- Improved: the score is lower than baseline
- Worsened: the score is higher than baseline

On IVMP, the number and percentage of participants will also be summarized by level at each visit for each dimension. Actual value and change from IVMP baseline in the VAS Score will be summarized on IVMP.

On DBTP, for each dimension, the number and percentage of participants will be summarized by level at each visit (as defined in 6.2.1.2). The percentage of Improvement/worsening/no change will be also displayed for the last analysis visits.
Shift tables will be created to summarize the number and proportion of participants with shifts from baseline levels to last assessment derived visit (as defined in 6.2.1.2) for each dimension by treatment group and overall.
Actual value and change from baseline in the VAS Score will be summarized on DBTP.

EQ-5D-5L data will be listed.

CAP-PRI

These analyses will be performed in SAF set.
The CAP-PRI questionnaire includes the assessment of 15 items. Items will be scored 0 (not at all), 1 (a little bit) or 2 (a lot). The total score will be calculated by adding the scores of each item yielding a total score that ranges from 0 to 30.
The CAP-PRI total score will be re-derived in ADaM for the analysis (refer to section 6.2.1.1 and appendix 9.3). If any item score is missing, the total score will be considered as missing.

On the IVMP, actual value and change from IVMP baseline of CAP-PRI total score will be summarized at each visit using descriptive statistics.

On the DBTP, Actual value and change from baseline of CAP-PRI total score at each visit (as defined in 6.2.1.2) will be summarized at each visit using descriptive statistics.

[redacted]

PGIC

These analyses will be performed in SAF set.

Responses to the Patient Global Impression of Change questionnaire range from 1 Very much improved to 7 Very much worse. Proportion of participants by level of improvement will be described at each visit and last assessment derived visit (as defined in 6.2.1.2). Cumulative percentage will be displayed from the worst to the best category by visit.

PGIC data will be listed.

FSS

These analyses will be performed in SAF.
The FSS consists of answering a short questionnaire that requires the participant to rate his or her own level of fatigue on 9 items and rated from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement. For the analysis, the average FSS score, calculated as the addition of all items divided by 9 will be provided.

The average FSS total score will be re-derived in ADaM for the analysis (refer to section 6.2.1.1 and appendix 9.3). If any item score is missing, the total score will be considered as missing.

On the IVMP, actual value and change from IVMP baseline of average FSS score at each visit will be summarized.

On the DBTP, actual value and change from baseline of average FSS score at each visit (as defined in 6.2.1.2) will be summarized.

FSS data will be listed.

6.5.3 Health-related Productivity and Work Productivity

These analyses will be performed in SAF set.

The HRPQ questionnaire consists of 21 questions. Questions assess absenteeism, presenteeism, and total percentage of work time loss due to MMN or its treatment during the past week for work output and household chores. The following items will be considered:

- **Number of scheduled hours**

- **Hours lost due to absenteeism**

The hours lost due to absenteeism is the number of hours missed form work.

- **Hours lost due to presenteeism**

The hours lost due to presenteeism will be calculated as follows:
Hours lost due to presenteeism= [(Scheduled hours - Hours missed form work) x (impact/100)]

- **Total hours lost (absenteeism and presenteeism)**

The total hours lost will be calculated as follows:
Total hours lost= Hours lost due to absenteeism + Hours lost due to presenteeism

- **Percent of scheduled hours lost due to absenteeism**

The percentage of scheduled hours lost due to absenteeism will be calculated as follows:

Percentage of scheduled hours lost due to absenteeism = (Hours missed form work / Scheduled hours) x 100.

- **Percent of scheduled hours lost due to presenteeism**

Percentage of scheduled hours lost due to presenteeism *= [Hours lost due to presenteeism / (Scheduled hours - Hours missed form work)] x 100*

If (Scheduled hours - Hours missed) form work is zero, then percent of scheduled hours lost due to presenteeism will be considered as missing.

- **Percent of total scheduled hours lost (due to absenteeism and presenteeism)**

Percentage of work time lost in total (ie, absenteeism and presenteeism) will be calculated as follows:

Percentage of work time lost in total= [(Hours lost due to presenteeism + Hours missed form work) / Scheduled hours] x 100

Each of these 6 variables will be derived for work output and household chores activities. These variables in relation to work output will be described only for employed participants while household chores activities variables will be described for all participants.

In case of scheduled hours < hours missed from work, then all the parameters for a same participant will be set to missing: number of scheduled hours, hours lost due to absenteeism, hours lost due to presenteeism, total hours lost (absenteeism and presenteeism), percent of scheduled hours lost due to absenteeism, percent of scheduled hours lost due to absenteeism, percent of scheduled hours lost due to presenteeism, percent of total scheduled hours lost (due to absenteeism and presenteeism).

A participant is considered employed if he/she is currently employed full-time or partially.

On IVMP, each variable will be described at each visit of the IVMP period.

On DBTP, each variable will be described at each visit and (as defined in 6.2.1.2) by treatment group and overall using descriptive statistics.

HRPQ questionnaire data will be listed.

6.5.4 Medication Treatment Satisfaction

These analyses will be performed using the SAF set.

The Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM-14) is divided into 4 subscales. These 4 subscales include the effectiveness subscale (items 1 to 3), the subscale side effects (items 4 to 8), the convenience subscale (items 9 to 11) and the global satisfaction subscale (items 12 to 14).

The (TSQM-14) scores for each subscale range from 0 to 100 with higher scores representing higher satisfaction on that domain.

On the IVMP, actual value of each subscale score at each visit will be summarized on the IVMP. The number of participants who had a side effect (ie, score item =1) will be provided as well for side effect domain.

For each subscale, the actual value at each visit (as defined in 6.2.1.2) will be summarized by treatment group and overall on the DBTP using descriptive statistics. The number of participants who had a side effect (ie, score item =1) will be provided as well for side effect domain.

Medication treatment satisfaction data will be listed.

6.5.5 Summary of Efficacy Endpoints

Two Efficacy summary tables will be presented for the following endpoints: mMRC-10 sum score, mMRC-14 sum score, average mMRC-14 sum score for the 2 most important muscle groups, GS 3-day moving average for most affected hand, GS 3-day moving average for less affected hand, MMN-RODs centile score, CAP-PRI and FSS:

- the change from baseline at last assessment before IVIg analysis visit by IVIg retreatment group for each efficacy endpoint.
- the change from baseline at last assessment before IVIg analysis visit by PGIC categories for each efficacy endpoint. PGIC categories will be defined as follows:
  - Improved: PGIC score is 1 2 or 3 at last assessment prior to IVIg retreatment
  - No change: PGIC score is 4 at last assessment prior to IVIg retreatment
  - Worsened: PGIC score is 5, 6 or 7 at last assessment prior to IVIg retreatment

6.6 Pharmacokinetic, Pharmacodynamics and Immunogenicity Evaluations

6.6.1 Pharmacokinetic Evaluation

Pharmacokinetic analyses will be performed on the pharmacokinetic populations and individual serum concentration summary statistics will be computed using all available PK data. All analyses will be performed by dosing regimen.

6.6.1.1 Serum concentrations

[redacted]

Individual serum ARGX-117 concentration data will be listed for each participant and summarized by nominal sampling time point, and visit as applicable with descriptive statistics

Individual serum ARGX-117 concentration-time data will be displayed graphically, summarized and listed.

Serum concentrations below the limit of quantification (BLQ): BLQ values will be flagged as BLQ in the concentration and parameters tables and considered to be 0 for calculation of PK parameters and descriptive statistical analysis. Listings will always present BLQ.

When more than half (>50%) of the values at a single time point are BLQ, the mean, median and minimum values are shown as "BLQ". The standard deviation (SD) and CV% are not calculated. Maximum values are reported as observed.

The BLQ handling is at the discretion of the PK scientist. Should BLQ handling be different from the above described processes, justification should be given.

[redacted]

Serum concentrations will be summarized by visit, time point and cohort including all scheduled sample assessments except if:

- the predose sample was taken after IMP administration;
- the IMP administration before the scheduled PK sample was missed (not applicable for day 1);
- PK samples are taken outside the visit windows as defined in **Error! Reference source not found.**.

6.6.1.2 Pharmacokinetic analyses

Pharmacokinetic analyses will be conducted using the PK set. PK parameters of ARGX-117 will be analyzed based on the actual sampling times. When actual times are not available, nominal times will be used instead if considered appropriate by the pharmacokineticist.

[redacted]

The following PK parameters will be calculated for ARGX-117 based on analysis visit:

Table 16 PK Parameters

Parameter (Units)	CDISC TERM	Definition	Method of Determination
$AUC_{0\text{-}72h}$[1] $AUC_{0\text{-}168h}$[2] $AUC_{0\text{-}336h}$	AUCINT	Area under the concentration versus time curve from 0 to 72 ,0 to 168 h, 0 to 336 h	Calculated using the linear up/log down variant of the trapezoidal rule
Cmax	CMAX	maximum observed serum concentration	Observed value
C72h[1] & C168h[2]	CMAX	concentration at 72 h for every week and 168 h for every 2-week dosing after dosing	Observed value
T_{max}	TMAX	time to reach Cmax	Observed value

[redacted]

All serum concentration data a will be displayed in listings.

PK Outliers

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the PK scientist following a review of the available documentation. Any such exclusion will be discussed with the sponsor and clearly documented in study report. Entire individual treatment profiles for a participant (or for a participant at a specific visit) may be excluded following review of the

available documentation and discussion with the sponsor. However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

6.6.2 Pharmacodynamics Evaluation

Free C2 (mg/L), total C2 (mg/L) and CH50 (Eq/mL) concentrations will be assessed. PD evaluations will be performed based on the PD set

- The actual value, change from baseline, percent change from baseline or each cohort, each day and time point will be summarized using descriptive statistics on IVMP and DBTP on the PD set.

  For DBTP only:
  - For Free C2, CH50 and Total C2, the maximum percent change from Baseline will be displayed
  - Free C2 and CH50, the maximum decrease from baseline and minimum postbaseline value will be derived during DBTP.
  - For Total C2, the maximum increase from baseline and maximum postbaseline value will be derived.

  For deriving maximum decrease from baseline, minimum post baseline value, maximum increase and maximum postbaseline value all postbaseline nonmissing values will be considered included unscheduled visits.

- PD values expressed as below the quantification limit will be imputed by the value of the quantification limit itself. The LLOQ for Free C2, CH50 and Total C2 are 0.049 mg/L, 0 Eq/mL and 0.78 mg/L respectively.
- PD values expressed as above the quantification limit will be imputed by maximum value of PD parameter or ULOQ itself, if available.

  For participants with a baseline PD value below/above the quantification limit, the PD parameter will be excluded from the statistical analysis involving change and percent change from baseline. Listings will always show the non imputed values

- When more than half (>50%) of the values at a single time point are BLQ, the mean, median and minimum values are reported BLQ. The SD, standard error (SE) and CV% are not calculated either. Maximum values are reported as observed.

Any potential impact of missing PD data or exclusion of the parameters from statistical analysis will be evaluated more closely during the data review process. Deviations from the presented calculation methods and data handling rules can be made, based on the discretion of the responsible PK/PD scientist and must be fully justified and documented.

6.6.3 Immunogenicity Evaluation

Blood samples will be collected for the determination of ADA to ARGX-117 (in serum samples) at the time points indicated in the schedule of activities (appendix 9.1).

Immunogenicity samples are analyzed in a 3-tiered approach:

- All samples are evaluated in the ARGX-117 ADA screening assay and are scored screening positive or negative
- If a sample scored screening positive, it is further evaluated in the confirmatory assay and is scored confirmed positive (positive immuno-depletion) or confirmed negative (negative immuno-depletion).
- If a sample is scored as confirmed positive, the samples are further characterized in the titration assay (to determine titer).

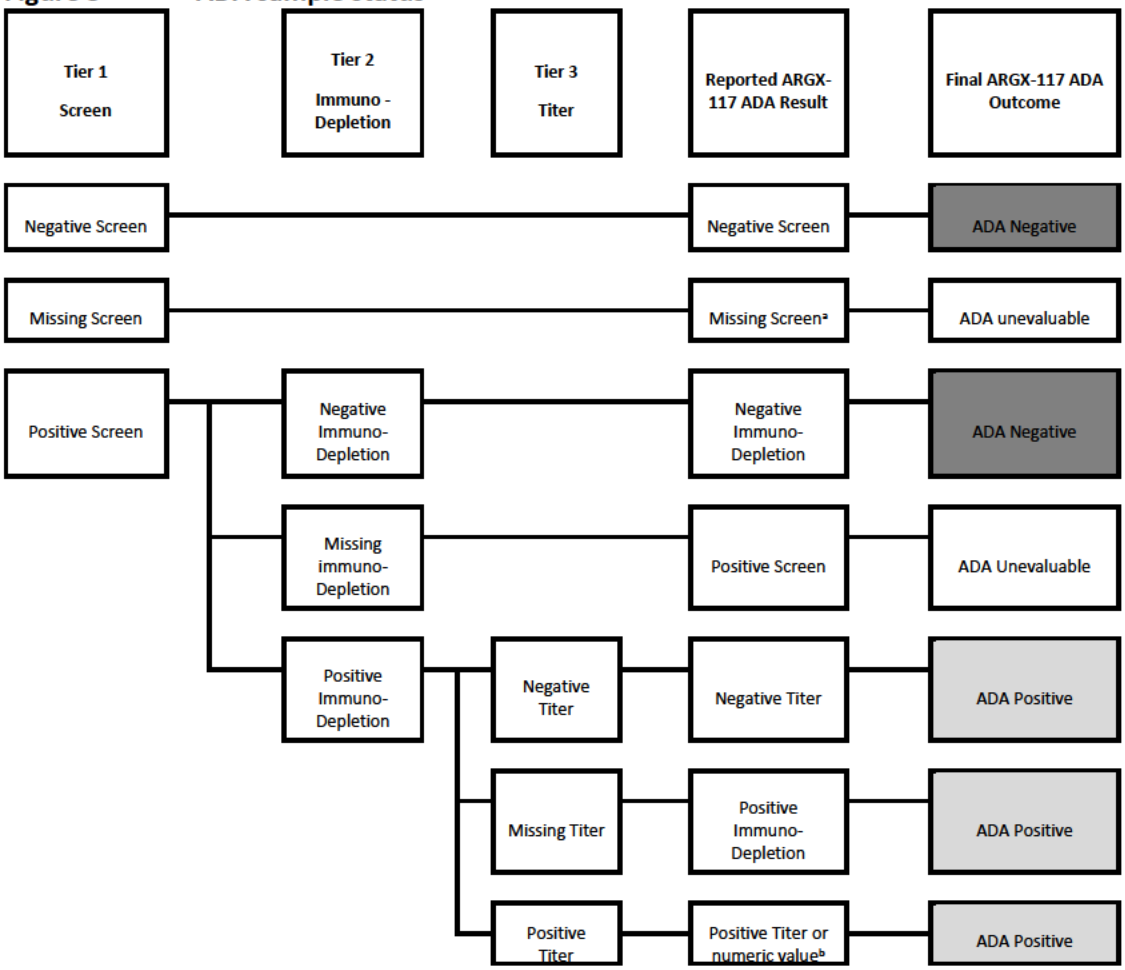
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

- In case the ADA confirmed positive sample could not be run in the titration assay (eg, due to insufficient sample volume/quality to perform the titer analysis), the result will be described as 'positive immuno-depletion' and the sample should be considered as ADA positive.
- If a sample is negative in the titration assay, it will be reported as 'negative titer' but it should be considered as ADA positive since it was confirmed positive in the second tier.
- If a sample could not be analyzed or reported as 'positive screen', the ADA sample status is ADA unevaluable.

An overview of this 3-tiered approach and all possible sample results that will be reported by the laboratory is given below (

Figure 3). From these reported ARGX-117 ADA sample results, a final sample status should be derived during the statistical analysis, as presented in the final column ('Final Outcome'):

Figure 3 ADA sample status



[a] missing screen includes the following terms (reported as reason not performed): NA (not analyzed), NR (no result), NS (no sample) and SL (sample lost). More details are provided in the IS Data Transfer Agreement from Celerion with Cytel.
[b] 'positive titer' is reported in case it was not possible to retrieve a numeric value.

Table below gives an overview of how the ADA participant classification for ARGX-117 will be derived, starting from the participant baseline ADA sample status.

Table 17 Participant Classification for ADA Against ARGX-117

	Highest[c] post baseline sample status				
Baseline ADA sample status	**ADA negative**	**ADA positive (missing titer[a])**	**ADA Positive (negative titer[b] or numerical titer value)**		**ADA Unevaluable**
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 numerical titer value)	Treatment-Unaffected ADA	ADA Unevaluable	titer < 4 x baseline titer: Treatment-Unaffected ADA	titer ≥ 4x baseline titer: Treatment-Boosted ADA	ADA Unevaluable
ADA Unevaluable	ADA Unevaluable	ADA Unevaluable	ADA Unevaluable		ADA Unevaluable

[a] Samples with missing titer have as reported ADA result 'positive immuno-depletion' or 'positive titer';

[b] Results reported as 'negative titer', ie, titer value < 100 will be set to 100

[c] Highest sample status, with order: (from low to high) : ADA unevaluable, ADA negative, ADA positive (missing titer /positive immuno-depletion), ADA positive with titer<100 ('negative titer') as reported ADA result, titer value set to 100), ADA positive with titer≥100 (ie, numerical value selecting the sample with highest titer)

ADA evaluable participant = participant classified as any of following categories according to

Table 17: ADA negative, treatment-unaffected ADA, treatment-induced ADA, treatment-boosted ADA. The first 2 categories are classified as 'ADA negative', the latter 2 as 'ADA positive'.

ADA unevaluable participant = participant classified as ADA unevaluable according to

Table 17 or with missing baseline ADA sample or without postbaseline ADA samples

Note: Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (= 2 times the dilution factor) (reference to Shankar et al., 2014).

The ADA incidence is defined as the percentage of participants with treatment-induced ADAs or treatment-boosted ADAs among the number of evaluable participants.

The ADA prevalence is defined as the percentage of participants with 'treatment-unaffected ADA', 'treatment-induced ADA' or 'treatment-boosted ADA' among the number of evaluable participants.

ADA analysis will be performed in the SAF set, combining data from DBTP and safety FU.

Frequency tabulations (Number and percentages) will be provided with ADA negative/positive/unevaluable samples per analysis visit and per ADA against ARGX-117 participant classification for each following treatment groups:

- ARGX-117 Dose Regimen 1
- ARGX-117 Dose Regimen 2 [redacted] if applicable
- ARGX-117 Dose Regimen 3 [redacted] if applicable
- Total ARGX-117
- Total Placebo

Frequency tabulations (Number and percentages) will be provided by treatment group and ARGX-117 combined on:

- Participants per ADA participant classification
- Prevalence and incidence of ADA
- ADA unevaluable participants
- ADA baseline positive / negative / unevaluable samples

ADA titer values against ARGX-117 will be summarized using descriptive statistics by ADA participant classification.

All immunogenicity data will be listed.

Correlation tables by ADA participant classification against ARGX-117 will be provided for the following parameters:

- Serum ARGX-117 concentration over time
- Concentration of free C2
- Percent change from baseline in free C2
- Concentration of total C2
- Percent change from baseline in total C2
- Concentration of CH50
- Percent change from baseline in CH50

- Overall Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Antidrug Antibodies Participant Classification (All Patients)
- Overall Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Antidrug Antibodies Participant Classification (All Patients)
- Overall Treatment-Emergent Hypersensitivity reaction(as defined in the 6.4.1 section) by Overall Antidrug Antibodies Participant Classification (All Patients)
- Overall Treatment-Emergent anaphylactic reaction (as defined in the 6.4.1 section) by Overall Antidrug Antibodies Participant Classification (All Patients)
- Treatment-Emergent Adverse Events of local reactions (as defined in the 6.4.1 section) by Overall Antidrug Antibodies Participant Classification
- Correlation tables on serum ARGX-117 concentration over time will be restricted to the ARGX-117 treated participants only (cohort 1 and cohort 2).

The other correlation tables must be provided for ARGX-117 (ie, cohort 1, cohort 2) and placebo treated participants (ie, total placebo).

[redacted]

[redacted]

7 CHANGES TO PLANNED ANALYSES

The changes between the protocol-defined statistical analyses and those presented in this statistical analysis plan are the following:

[redacted] All participants from cohort 2 will be included in the analysis (even ongoing participants) and will be unblinded.

The following endpoints were added:

[redacted]

- [redacted]

Statistical Analysis

[redacted]

- [redacted]
- [redacted]

For mMRC-14, MMN-RODS, and CAP-PRI, ANCOVA were added to estimate treatment effect on these parameters.

Description of placebo groups within each cohort were added, in addition to the pooled placebo group (placebo from cohort 1 and placebo from cohort 2).

Description of the change from baseline before IVIg retreatment by IVIg retreatment group and PGIC category, by cohort and overall were added for the following efficacy endpoints: mMRC-10 sum score, mMRC-14 sum score, average mMRC-14 sum for the 2 most important muscle groups, Grip Strength 3 day moving average (most / less) affected hand, MMN-RODS centile score and CAP-PRI total score.

8 REFERENCES

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9 APPENDICES

9.1 Schedule of Activities

Table 18 IVIg Dependency and IVIg Monitoring Period Schedule of Activities Through Day −7

	IVIg Dosing Frequency	SCN[a]	IVIg Dependency[b]		IVIg Monitoring[c]		
Visit (Days)		**Up to 28 days**	**IDV1[d]**	**IDV2[b]**	**IMV1[f]**	**IMV2**	**IMV3**
	Q 2 weeks		**1**	**29**	**1**	**15**	**29**
	Q 3 weeks		**1**	**43**	**1**	**22**	**43**
	Q 4 weeks		**1**	**57**	**1**	**29**	**57**
	Q 5 weeks		**1**	**71**	**1**	**36**	**71**
Visit Window (Days)				**±7**	**±3**	**±3**	**±3**
Activity							
Informed consent		X					
Inclusion/exclusion criteria check		X			X		
MCC confirmation		X			X		
SARS-CoV-2 antigen test*		X	X	X	X	X	X
Medical history		X					
Demography		X					
Pregnancy test[c]		X			X		
FSH level[d]		X					
Physical examination[e]		X	X	X	X	X	X
Vital sign measurements[f]		X	X	X	X	X	X
12-lead ECG(s)[g]		X				X	X
SIB risk and monitoring[h]		X	X	X	X	X	X
Samples for safety laboratory tests		X	X	X	X	X	X
Samples for SLE panel[i]		X					

	IVIg Dosing Frequency	SCN[a]	IVIg Dependency[b]		IVIg Monitoring[c]		
Visit (Days)		Up to 28 days	IDV1[d]	IDV2[b]	IMV1[f]	IMV2	IMV3
	Q 2 weeks		1	29	1	15	29
	Q 3 weeks		1	43	1	22	43
	Q 4 weeks		1	57	1	29	57
	Q 5 weeks		1	71	1	36	71
Visit Window (Days)				±7	±3	±3	±3
Activity							
Samples for urinalysis		X					X

	IVIg Dosing Frequency	SCN[Error! Reference source not found.]	IVIg Dependency[b]		IVIg Monitoring[c]		
Visit (Days)		Up to 28 days	IDV1[d]	IDV2[e]	IMV1[f]	IMV2	IMV3
	Q 2 weeks		1	29	1	15	29
	Q 3 weeks		1	43	1	22	43
	Q 4 weeks		1	57	1	29	57
	Q 5 weeks		1	71	1	36	71
Visit Window (Days)				±7	±3	±3	±3
Activity							
Samples for pharmacodynamics[j]			X	X	X	X	X
Samples for immunogenicity[k]		X					
Biomarkers[l]					X	X	X
Virology screen		X					
Pharmacogenetic sample		X[m]					
[redacted]							

	IVIg Dosing Frequency	SCN[Error! Reference source not found.]	IVIg Dependency[b]		IVIg Monitoring[c]		
Visit (Days)		Up to 28 days	IDV1[d]	IDV2[e]	IMV1[f]	IMV2	IMV3
	Q 2 weeks		1	29	1	15	29
	Q 3 weeks		1	43	1	22	43
	Q 4 weeks		1	57	1	29	57
	Q 5 weeks		1	71	1	36	71
Visit Window (Days)				±7	±3	±3	±3
Activity							
[redacted]							
Research sample[r]					X[o]	X[s]	X[s]
IVIg administration[p]			X	X	X	X	X
Grip strength[q]		X	Continuous Monitoring				
MMN-RODS		X	X	X	X	X	X
mMRC		X	X	X	X	X	X
9-HPT		X	X	X	X	X	X
HRPQ					X	X	X
EQ-5D-5L					X	X	X
CAP-PRI					X	X	X
FSS					X	X	X

9-HPT=9-Hole Peg Test; ANA=antinuclear antibody; BMI=body mass index; CAP-PRI=chronic acquired polyneuropathy patient-reported index; C-SSRS=Columbia- suicide severity rating scale; DBTP=double-blinded treatment period; dsDNA=double stranded DNA; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; EQ-5D-5L=Euro-Quality of Life 5 Dimensions 5 Levels; FSH=follicle-stimulating hormone; FSS=fatigue severity scale; [redacted] HRPQ=Health-Related Productivity Questionnaire; IDV=IVIg dependency visit; IMP=investigational medicinal product; IMV=IVIg monitoring visit; INR=international normalized ratio; IVDP=IVIg dependency period; IVIg=intravenous immunoglobulin; IVMP=IVIg monitoring period; MCC=MMN Confirmation Committee; MMN=multifocal motor neuropathy; MMN-RODS=Rasch-built overall disability scale for MMN; mMRC=modified Medical Research Council; NAbs=neutralizing antibodies; [redacted] PD=pharmacodynamic(s); PE=physical examination; PHQ-9=patient health questionnaire 9 depression questionnaire; Q=every; SCN=screening period; SIB=suicidal ideation and behavior; SLE=systemic lupus erythematosus; SNP=single nucleotide polymorphism; TSQM=Treatment Satisfaction 14-item Questionnaire for Medication

Note: All assessments will be performed before IVIg administration unless otherwise specified.

* **For Germany only:** A SARS-CoV-2 rapid antigen test must be completed or a negative rapid antigen test not older than 48 hours (depending on local requirements) must be presented upon site entry for each visit. The antigen test must be negative before the visit can begin. Rapid antigen testing will only be mandatory if required locally.

[a] The screening period is 1 to 28 days before the IVMP or the IVDP. The scheduled time of visit is variable based on the participant's IVIg dose regimen retrieved from their medical record (inclusion criterion 5.1a). The screening period may be extended by an additional 14 days to a total of 42 days with the written approval of the medical monitor.

[b] The IVDP, if applicable, occurs up to 15 weeks (105 days) before the IVMP.

[c] The IVMP occurs up to 11 weeks before day 1 of the DBTP.

[d] IDV1 will coincide with the participant's regularly scheduled IVIg administration.

[e] Participants will have an earlier visit than planned if they demonstrate a clinically meaningful deterioration between the scheduled visits of the IVDP. This visit will be considered IDV2.

[f] IMV1 will coincide with the participant's regularly scheduled IVIg administration and will be the participant's next regularly scheduled IVIg visit after IDV2 if they entered the IVDP. The visit window for IMV1 is not applicable if the participant does not enter the IVDP.

[g] Female participants will have a serum pregnancy test performed at screening. A urine pregnancy test will be performed at IMV1 for women of childbearing potential.

[h] FSH levels will be measured at screening for all female participants.

[i] The PE will include the parameters specified in Section 8.2.1 of the protocol.

[j] Weight, height, and BMI calculation will be performed at screening. Weight will also be measured at IMV3 and used to calculate the dose for all IMP administrations.

[k] Triplicate 12-lead ECGs will be performed during screening and at V1. A single 12-lead ECG will be performed at all other scheduled time points.

[l] The C-SSRS will be used to assess the risk of suicidal ideation at screening. SIB risk monitoring will be based on question 9 of the PHQ-9 at all other scheduled time points.

[m] An ANA test will be performed at screening, the titer and staining pattern will be reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) will be evaluated from the blood samples collected. The presence of ENA autoantibodies will only be reported if ANA ≥1:100.

[n] Samples should be collected before IVIg is administered.

[o] Immunogenicity assessments will be performed predose of IVIg administration.

[p] [redacted].

[q] A blood sample for SNP analysis will be collected at this time point.

[r] Samples must be collected before IVIg is administered.

[s] A research sample will be collected during the IVIg monitoring period (visits IMV1-IMV3). This sample should be collected predose and postdose of the IVIg administration. This sample should be collected immediately after the end of the IVIg administration, regardless of the duration (after the last hour or day) of the administration.

[t] IVIg will be administered during the IVIg dependency and IVMP at the time points scheduled. IVIg may be administered over several days according to the local standard of care. All IVIg administrations must occur within the specified visit windows.

[u] Grip strength will be measured on-site at all study visits and monitored daily starting from the IVDP or IVMP.

[v] Adverse events and concomitant medications/procedures will be monitored continuously from receipt of informed consent signature until the last study-related activity. All available vaccination history should be recorded.

Table 19 IMP Administration Period Schedule of Activities, [redacted]

Activity															
Inclusion/exclusion criteria check	X														
SARS-CoV-2 antigen test*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Pregnancy teste	X					X		X			X	X		X		(X)
Physical examination [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Vital sign measurements [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
12-lead ECG(s) [h]	X							X						X		(X)
SIB risk and monitoring[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Samples for safety laboratory tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)

[redacted]															
Activity															
Samples for SLE panel[j]	X							X						X		(X)
Samples for urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Samples for pharmacokinetics[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Samples for pharmacodynamics[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
[redacted]															
Samples for immunogenicity[m]	X			X		X		X			X			X	X	(X)
[redacted]															
Pharmacogenetic sample[o]	X															

[redacted]

Activity																
[redacted]																
[redacted]																
Research sample[p]				X		X								X		(X)
Randomization	X															
Eligibility confirmation and decision to roll over into the LTE														X		
IVIg retreatment[q]	X															
[redacted]																
Grip strengths	Continuous monitoring															
MMN-RODS	X		X	X	X	X	X	X	X		X	X		X	X	(X)
mMRC	X		X	X	X	X	X	X	X		X	X		X	X	(X)

[redacted]

Activity																
9-HPT	X		X	X	X	X	X	X	X		X	X		X	X	(X)
HRPQ	X			X		X		X			X			X	X	(X)
EQ-5D-5L	X			X		X		X			X			X	X	(X)
CAP-PRI	X			X		X		X			X			X	X	(X)
FSS	X			X		X	X	X	X		X	X		X	X	(X)
14-item TSQM	X			X		X	X	X	X		X	X		X	X	(X)
PGIC	X			X		X	X	X	X		X	X		X	X	(X)
Concomitant medication/ procedurest	Continuous monitoring															
Adverse events[t]	Continuous monitoring															

9-HPT=9-Hole peg test; ANA=anti-nuclear antibody; BMI=body mass index; CAP-PRI=chronic acquired polyneuropathy patient-reported index; C-SSRS=Columbia suicide severity rating scale; dsDNA=double stranded DNA; DBTP=double-blinded treatment period; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; ED=early discontinuation; EQ-5D-5L= Euro-Quality of Life 5 Dimensions 5 Levels; FSS=fatigue severity scale; HRPQ=health-related productivity questionnaire; IMP=investigational medicinal product; IMV=IVIg monitoring visit; INR=international normalized ratio; IV= intravenous; IVIg=intravenous immunoglobulin; LTE=long-term extension; MMN=multifocal motor neuropathy; MMN-RODS=Rasch-built overall disability scale for MMN; mMRC=modified Medical Research Council; NAbs=neutralizing antibodies; [redacted] PD=pharmacodynamic(s); PE=physical examination; PGIC=patient global impression change; PHQ-9=patient health questionnaire 9 depression questionnaire; PK=pharmacokinetic(s); SIB=suicidal ideation and behavior; SLE=systemic lupus erythematosus; TSQM=Treatment Satisfaction 14-item Questionnaire for Medication; UNS=unscheduled; V=visit

Note: Participants who do not elect to enroll in the long-term extension study will have additional follow-up visits described in Table 3

Note: All assessments will be performed before IMP or IVIg administration unless otherwise specified.
Note: V1 will be 7 days after the final day of IVIg administration for IMV3 (Table 1)
* For Germany only: A SARS-CoV-2 rapid antigen test must be completed or a negative rapid antigen test not older than 48 hours (depending on local requirements) must be presented upon site entry for each visit. The antigen test must be negative before the visit can begin. Rapid antigen testing will only be mandatory if required locally.
a [redacted].
b The assessments in this visit are for participants who complete the DBTP and participants who discontinue prematurely after randomization (ie, ED visit). The activities and assessments for the participants who roll over to the LTE will be provided in the ARGX-117-2003 LTE protocol.
c Participants who demonstrate a clinical deterioration during the DBTP may be re-treated with IVIg. A UNS IVIg visit will be performed at the participant's first occurrence of clinical deterioration necessitating retreatment with IVIg. If the timing for subsequent IVIg retreatment does not coincide with a regularly scheduled visit day of the DBTP, a UNS visit will be performed for the participant to receive IVIg.
d A UNS visit can occur at the request of the investigator and additional assessments can be performed at the discretion of investigator. (X) indicates that the assessment will be performed at the discretion of the investigator.
e A urine pregnancy test will be performed at V1, V6, V8, V11, V12, V14/ED and at any UNS visits for women of childbearing potential.
f The PE will include the parameters specified in Section 8.2.1 of the protocol.
g The weight measured at IMV3 will be used to calculate the dose for all IMP administrations.
h Triplicate 12-lead ECGs will be performed during screening and at V1. A single 12-lead ECG will be performed at all other scheduled time points.
i The C-SSRS will be used to assess the risk of suicidal ideation at screening. SIB risk monitoring will be based on question 9 of the PHQ-9 at all other scheduled time points.
j An ANA test will be performed at the specified time points, the titer and staining pattern will be reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, anti-phospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) will be evaluated from the blood samples collected. The presence of ENA autoantibodies will only be reported if ANA ≥1:100.
k PK and PD assessments on day 1 will be performed predose, 2 hours, and 6 hours postdose of the IMP infusion. Detailed schedules for collecting blood samples for PK and PD analyses are provided in Table 4 and Table 5.
l . A detailed schedule for collecting blood samples for cytokine analyses is provided in Table 23.
m Immunogenicity assessments will be performed predose of IMP administration.
n [redacted]
o Sample collection is optional.
p Samples must be collected predose on days when IMP or IVIg are administered.
q IVIg will be administered to participants demonstrating a meaningful clinical deterioration.
r IMP will be administered as an IV infusion over approximately 2 hours at V1. IMP will be administered over approximately 1 hour at all other scheduled time points. Participants will be monitored for at least 1 hour after the end of the infusion.
s Grip strength will be measured on-site at all visits and monitored daily.
t Adverse events and concomitant medications/procedures will be monitored continuously from receipt of informed consent signature until the last trial-related activity. All available vaccination history should be recorded as part of the participant's prior medication for vaccination received in the past, or as concomitant medication for vaccinations received during the trial.

Table 20 Follow-up Period Schedule of Activities

	Follow-up Period					
Visit	**FUV1**	**FUV2**	**FUV3**	**FUV4**	**FUV5**	**FUV6/EOT**
Time of Visit (Weeks)	**W4**	**W12**	**W24**	**W36**	**W52**	**W64**
Visit Window (Weeks)		**±1**			**±2**	
SARS-CoV-2 antigen test*	X	X	X	X	X	X
Pregnancy test[a]	X	X	X	X	X	X
Physical examination[b]	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X
12-lead ECGs[d]		X		X		X
Samples for safety laboratory tests	X	X	X	X	X	X
Samples for SLE panel[e]		X	X	X	X	X
Samples for urinalysis	X	X	X	X	X	X
Samples for pharmacokinetics	X	X	X	X	X	X
Samples for pharmacodynamics	X	X	X	X	X	X
Samples for immunogenicity		X	X	X	X	X
[redacted]						

	Follow-up Period					
Visit	**FUV1**	**FUV2**	**FUV3**	**FUV4**	**FUV5**	**FUV6/EOT**
Time of Visit (Weeks)	**W4**	**W12**	**W24**	**W36**	**W52**	**W64**
Visit Window (Weeks)		**±1**			**±2**	
[redacted]						
Research sample		X	X	X	X	X
Concomitant medication/procedures[f]	Continuous monitoring					
Adverse events[f]	Continuous monitoring					

ANA=antinuclear antibody; ECG=electrocardiogram; ENA=extractable nuclear antigen antibodies; EOT=end of trial; FUV=follow-up visit; INR=international normalized ratio; IVIg=intravenous immunoglobulin; LTE=long-term extension; [redacted]; PD=pharmacodynamic(s); PE=physical examination; PK=pharmacokinetic(s); SLE=systemic lupus erythematosus; W=week

Note: The follow-up period is not applicable for participants who roll over into the LTE.

[redacted]

* **For Germany only:** A SARS-CoV-2 rapid antigen test must be completed or a negative rapid antigen test not older than 48 hours (depending on local requirements) must be presented upon site entry for each visit. The antigen test must be negative before the visit can begin. Rapid antigen testing will only be mandatory if required locally.

[a] A urine pregnancy test will be performed at the scheduled time points for women of childbearing potential.

[b] The PE will include the parameters specified in Section 8.2.1 of the protocol.

[c] Vital signs will include the measurements described in Section 8.2.2 of the protocol.

[d] 12-lead ECGs will be performed as described in Section 8.2.3 of the protocol.

[e] An ANA test will be performed at the specified time points, the titer and staining pattern will be reported; the potential presence of ENA autoantibodies (anti-dsDNA, anti-Smith, antiphospholipid (anti-cardiolipin IgG and anti-beta-2-glycoprotein IgG), anti-Ro (anti-Ro52 and anti-Ro60), anti-La and anti-U1RNP) will be evaluated from the blood samples collected. The presence of ENA autoantibodies will only be reported if ANA ≥1:100.

f Adverse events, and concomitant medications/procedures will be monitored continuously from receipt of informed consent signature until the last trial-related activity. IVIg administered throughout the safety follow-up period will be monitored as a concomitant medication. All available vaccination history should be recorded as part of the participant's prior medication for vaccination received in the past, or as concomitant medication for vaccinations received during the trial.

Table 21 Blood Collection Schedule for PK and PD Analyses

[redacted]

IMP=investigational medicinal product; PD=pharmacodynamic; PK=pharmacokinetic; V=visit

[a] Day 4 (V2) is not mandatory and is considered an optional visit. A minimum of 14 participants per cohort are targeted to attend the optional visits.
[b] Blood samples will be collected from the participant before the start of the IMP administration.
[c] The timing of postdose sample collection is relative to the start of the IMP infusion.
[d] Blood samples will be collected immediately at the end of the infusion.

Table 22 Blood Collection Schedule for PK and PD Analyses

[redacted]

Table 23 Blood Collection Schedule

[redacted]

9.2 List of Tables, Figures and Listings

9.2.1 Tables and Figures

Table 24 List of Tables and Figures

TABLE/ FIGURE	NUMBER	TITLE	Interim Analysis 1 (cohort 1)	Interim Analysis 2 (cohort 1 + cohort 2)	Final analysis (cohort 1 + cohort 2)
GENERAL CHARACTERISTICS					
Table	14.1.1	Overall Disposition - Enrolled Set	x	x	x
Table	14.1.2	Overall Disposition - Safety Set	x	x	x
Table	14.1.3	Participants Disposition - by Country and Site - Enrolled Set	x	x	x
Table	14.1.4	Participants Disposition by Country and Site - Safety Set	x	x	x
Table	14.1.5	Study Periods Duration - Safety Analysis Set	x	x	x
Table	14.1.6	Protocol Deviations - Safety Set		x	x
Table	14.1.7	Overview of Analysis Sets - Enrolled Set	x	x	x

Table	14.1.8	Demographic and Baseline Characteristics - Safety Set	x	x	x
Table	14.1.9	Medical History - Safety Set		x	x
Table	14.1.10	MMN Disease History - Safety Set	x	x	x
Table	14.1.11	Confirmation of Diagnosis and IVIg Dependency by MCC - Safety Set	x	x	x
Table	14.1.12	IVIg History - Safety Set	x	x	x
Table	14.1.13	IVIg Treatment during IVMP - Safety Set	x	x	x
Table	14.1.14	Prior Medications - Safety Set		x	x
Table	14.1.15	Prior Procedures - Safety Set		x	x
Table	14.1.16	Summary of concomitant medications during DBTP - Safety Set		x	x
Table	14.1.17	Summary of concomitant procedures during DBTP - Safety Set		x	x
Table	14.1.18	IMP Exposure and Compliance - Safety Set		x	x
Table	14.1.19	Summary of DBTP Baseline Scores for Efficacy Endpoints		x	x
EFFICACY					
Table	14.2.1.1	Time to First Retreatment with IVIg during DBTP [1] - Safety Set	x	x	x

Figure	14.2.1.2	Time to First Retreatment with IVIg - Safety Set	x	x	x
Table	14.2.1.3	Time to Relapse during DBTP - Safety Set	x	x	x
Figure	14.2.1.4	Time to Relapse during DBTP - Safety Set	x	x	x
Table	14.2.1.5	Retreatment with IVIg during the DBTP - Safety Set	x	x	x
Table	14.2.1.6	Retreatment with IVIg Status according to Worsening status during DBTP - Safety Set	x	x	x
Table	14.2.1.7	Retreatment with IVIg Status according to Worsening status during DBTP - Safety Set	x	x	x
Table	14.2.1.8	Summary of mMRC-10 Sum Score during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.9	Summary of mMRC-10 Sum Score during IVMP and DBTP by IVIg Dose Frequency Subgroup - Safety Set	x	x	x
Table	14.2.1.10	mMRC-10 Sum Score during DBTP - Analysis of Covariance - Trial-product strategy [1] - Safety Set	x	x	x
Table	14.2.1.11	mMRC-10 Sum Score during DBTP - Analysis of Covariance - Treatment-policy strategy [1] - Safety Set	x	x	x
Table	14.2.1.12	Summary of net iAUC per week of mMRC-10 Sum Score during DBTP - Safety Set	x	x	x
Table	14.2.1.14	Deterioration of at least 2 points as assessed by mMRC-10 Sum Score at Last Assessments - Safety Set	x	x	x
Table	14.2.1.16	Summary of mMRC-14 Sum Score during IVMP and DBTP - Safety Set	x	x	x
Table	14.1.2.17	Summary of mMRC-14 Sum Score during IVMP and DBTP by IVIg Dose Frequency Subgroup - Safety Set	x	x	x

Table	14.2.1.18	mMRC-14 Sum Score during DBTP - Analysis of Covariance - - Trial-product strategy [1] - Safety Set	x	x	x
Table	14.2.1.19	mMRC-14 Sum Score during DBTP - Analysis of Covariance - Treatment-policy strategy [1] - Safety Set	x	x	x
Table	14.2.1.24	Summary of the Average mMRC-14 Scores for the two Most Important Muscle Groups during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.25	Summary of the Average mMRC-14 Scores for the two Most Important Muscle Groups during DBTP by IVIg Dose Frequency Group - Safety Set	x	x	x
Table	14.2.1.26	Summary of GS Daily Average at Last Assessment during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.27	Summary of GS Daily Average at Last Assessment by IVIg Dose Frequency Subgroup during DBTP - Safety Set	x	x	x
Table	14.2.1.28	GS Daily Average - Analysis of Covariance - Trial-product Strategy [1] - Safety Set	x	x	x
Table	14.2.1.29	GS Daily Average - Analysis of Covariance Treatment policy strategy [1] - Safety Set	x	x	x
Table	14.2.1.30	Summary of net iAUC per week of GS Daily Average during DBTP - Safety Set	x	x	x
Table	14.2.1.34	Summary of GS 3-Day Moving at Last Assessment during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.35	Summary of GS 3-Day Moving at Last Assessment by IVIg Dose Frequency Subgroup during DBTP - Safety Set	x	x	x
Table	14.2.1.36	GS 3-Day Moving Average - Analysis of Covariance - Trial-product strategy [1] - Safety Set	x	x	x

Table	14.2.1.37	GS 3-day Moving - Analysis of Covariance - Treatment-policy strategy [1] - Safety Set	x	x	x
Table	14.2.1.38	GS 3-day Moving Average Decrease of more than 30% from baseline over 2 consecutive days at Last Assessment during DBTP - Safety Set	x	x	x
Table	14.2.1.39	GS 3-day Moving Average Decrease of more than 30% from baseline over 2 consecutive days at Last Assessment before IVIg during DBTP -Safety Set	x	x	x
Table	14.2.1.41	Summary of MMN-RODS Score (centile metric) during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.42	Summary of MMN-RODS (centile metric) by IVIg Dose Frequency Subgroup during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.43	Summary of MMN-RODS Score (total raw score) during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.45	MMN-RODS Score (centile metric) during DBTP - Analysis of Covariance - Trial-product strategy [1] - Safety Set	x	x	x
Table	14.2.1.46	MMN-RODS Score (centile metric) during DBTP - - Analysis of Covariance - Treatment-policy strategy [1] - Safety Set	x	x	x
Table	14.2.1.47	Average time required to complete 9-HPT during IVMP and DBTP (seconds) - Safety Set	x	x	x
Table	14.2.1.48	Average time required to complete 9-HPT (seconds) by IVIg Dose Frequency Subgroup during IMVP and DBTP - Safety Set	x	x	x
Table	14.2.1.51	Summary of EQ-5D-5L Domains during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.52	EQ-5D-5L Domains - Shift from Baseline to Post Baseline Visit during DBTP - Safety Set	x	x	x
Table	14.2.1.53	Summary of EQ-5D-5L VAS during IVMP and DBTP - Safety Set	x	x	x

Table	14.2.1.54	Summary of CAP-PRI Total Score during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.55	CAP-PRI Total Score during DBTP - Analysis of Covariance - Trial-product strategy [1] - Safety Set		x	x
Table	14.2.1.56	CAP-PRI Total Score during DBTP - Analysis of Covariance – Trial - policy strategy [1] - Safety Set		x	x
Table	14.2.1.57	Summary of PGIC during DBTP - Safety Set	x	x	x
Table	14.2.1.58	Summary of FSS average score during IVMP and DBTP - Safety Set	x	x	x
Table	14.2.1.59	Summary of HRPQ during IVMP and DBTP - Work Activities (employed or partially employed patients) - Safety Set	x	x	x
Table	14.2.1.60	Summary of HRPQ during IVMP and DBTP - Household Chores Activities - Safety Set	x	x	x
Table	14.2.1.61	Summary of TSQM-14 scores during DBTP - Safety Set	x	x	x
Table	14.2.1.62	Summary of Efficacy Parameters at last assessment DBTP prior to IVIg retreatment by IVIg retreatment group – Safety Set		x	x
Table	14.2.1.63	Summary of Efficacy Parameters at last assessment DBTP prior to IVIg retreatment by PGIC category – Safety Set		x	x
PHARMACOKINETICS					
Table	14.2.2.1	Summary of Serum Pharmacokinetic Parameters Following Administration of EMPASIPRUBART Following Administration of EMPASIPRUBART - PK Set		x	x
Table	14.2.2.2	Individual and Descriptive Statistical Summary: Serum Pharmacokinetics Parameters Following Administration of EMPASIPRUBART - PK Set		x	x

Table	14.2.2.3	Individual Values and Descriptive Statistical Summary: Serum Concentrations Following Administration of EMPASIPRUBART - PK Set		x	x
PHARMACODYNAMICS					
Table	14.2.3.1	Summary of Free C2 Concentrations <unit> during IMVP and DBTP - PD set		x	x
Table	14.2.3.3	Summary of Total C2 Concentrations <unit> during IVMP and DBTP - PD set		x	x
Table	14.2.3.5	Summary of CH50 Concentrations <unit> during IVMP and DBTP - PD set		x	x
IMMUNOGENICITY					
Table	14.2.4.1	ADA against EMPASIPRUBART Classification by Visit during DBTP and Safety Follow-up Period - Safety Set		x	x
Table	14.2.4.2	Incidence and Prevalence of ADA against EMPASIPRUBART during DBTP and Safety Follow-up Period - Safety Set		x	x
Table	14.2.4.3	Summary of ADA against EMPASIPRUBART Titer Values by ADA Participant Classification against ARGX-117 by Visit during DBTP and Safety Follow-up Period - Safety Set		x	x
Table	14.2.4.4	Empasiprubart concentration over time by ADA participant classification against EMPASIPRUBART - <Treatment Group> - PK Set		x	x
Table	14.2.4.5	Free C2 concentrations over time by ADA participant classification against Empasiprubart - <Treatment Group: > - PD Set		x	x
Table	14.2.4.6	Percent change from baseline in free C2 by ADA participant classification against Empasiprubart - <Treatment Group> - PD Set		x	x

Table	14.2.4.7	Total C2 concentrations over time by ADA participant classification against Empasiprubart - <Treatment Group> - PD Set		x	x
Table	14.2.4.8	Percent change from baseline in total C2 by ADA participant classification against Empasiprubart - <Treatment Group> - PD Set		x	x
Table	14.2.4.9	CH50 concentrations over time by ADA participant classification against Empasiprubart - <Treatment Group> - PD Set		x	x
Table	14.2.4.10	Percent change from baseline in functional complement activity (CH50) by ADA participant classification against Empasiprubart - <Treatment Group> - PD Set		x	x
Table	14.2.4.11	Overall Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Antidrug Antibodies Participant Classification - <Treatment group> - Safety Set		x	x
Table	14.2.4.12	Overall Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Antidrug Antibodies Participant Classification - <Treatment group> - Safety Set		x	x
Table	14.2.4.13	Overall Treatment-Emergent Adverse Events of Hypersensitivity by Overall Antidrug Antibodies Participant Classification - <Treatment group> -Safety Set		x	x
Table	14.2.4.14	Overall Treatment-Emergent Adverse Events of Anaphylactic Reaction by Overall Antidrug Antibodies Participant Classification - <Treatment group> -Safety Set		x	x
Table	14.2.4.15	Overall Treatment-Emergent Adverse Events of Local Reaction by Overall Antidrug Antibodies Participant Classification - <Treatment group> -Safety Set		x	x
[redacted]					

[redacted]	[redacted]	[redacted]			
ADVERSE EVENTS					
Table	14.3.1.1	Overview of Treatment-Emergent Adverse Events during DBTP - Safety Set	x	x	x
Table	14.3.1.2	Overview of Treatment Emergent Adverse Events from start of DBTP up to the end of Safety Follow-up period - Safety Set		x	x
Table	14.3.1.3	Treatment Emergent Adverse Events by SOC and PT during DBTP - Safety Set	x	x	x
Table	14.3.1.4	Treatment Emergent Adverse Events Related to IMP by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.5	Treatment Emergent Adverse Events Related to IVIg by SOC and PT during DBTP -Safety Set		x	x
Table	14.3.1.6	Treatment Emergent Adverse Events Related to Procedure by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.7	Serious Treatment Emergent Adverse Events by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.8	Serious Treatment Emergent Adverse Events Related to IMP by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.9	Non Serious Treatment Emergent Adverse Events by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.10	Treatment Emergent Adverse Events Leading to Withdrawal of IMP by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.11	CTCAE Grade 3 or Higher Treatment Emergent Adverse Events by SOC and PT during DBTP -Safety set		x	x

Table	14.3.1.12	Treatment Emergent Adverse Events of Special Interest by SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.13	Treatment Emergent Adverse Events by Worst CTCAE Grade SOC and PT during DBTP - Safety Set		x	x
Table	14.3.1.14	Treatment Emergent Adverse Events of Hypersensitivity Reaction during DBTP - Safety Set		x	x
Table	14.3.1.15	Treatment Emergent Adverse Events of Anaphylactic Reaction during DBTP - Safety Set		x	x
Table	14.3.1.16	Treatment Emergent Adverse Events of Local Reaction during DBTP - Safety Set		x	x
Table	14.3.1.17	Treatment Emergent Adverse Events by SOC and PT from start of DBTP up to the end of Safety Follow-up Period - Safety Set		x	x
LABORATORY					
Table	14.3.4.1.1	Blood Chemistry: Summary of Laboratory Test Results and Change from Baseline by Visit during DBTP - Safety Set		x	x
Table	14.3.4.1.2	Blood Chemistry - Shift Table of Reference Ranges versus Baseline during DBTP - Safety Set		x	x
Table	14.3.4.1.3	Blood Chemistry - Shift Table of Laboratory Toxicity Grades versus Baseline during DBTP - Safety Set		x	x
Table	14.3.4.1.4	Hematology: Summary of Laboratory Test Results and Change from Baseline by Visit during DBTP - Safety Set		x	x
Table	14.3.4.1.5	Hematology - Shift table of Reference Ranges versus Baseline during DBTP - Safety Set		x	x
Table	14.3.4.1.6	Hematology - Shift table of Laboratory Toxicity Grades versus Baseline during DBTP - Safety Set		x	x

Table	14.3.4.1.7	Coagulation: Summary of Laboratory Test Results and Change from Baseline by Visit during DBTP and Safety Follow-up period - Safety Set		x	x
Table	14.3.4.1.8	Coagulation - Shift table of References Ranges versus Baseline on Clinical Findings during DBTP and Safety Follow-up period Period - Safety Set		x	x
Table	14.3.4.1.9	Urinalysis: Summary of Laboratory Test Results and Change from Baseline by Visit during DBTP - Safety Set		x	x
Table	14.3.4.1.10	Urinalysis - Shift table of Reference Ranges versus Baseline during DBTP - Safety Set		x	x
Table	14.3.4.1.11	Antinuclear Antibodies (ANA) - Proportions by Categories during DBTP - Safety Set		x	x
Table	14.3.4.1.12	Antinuclear Antibodies (ANA) - Shift table of ANA categories versus Baseline during DBTP - Safety Set		x	x
VITAL SIGNS					
Table	14.3.4.2.1	Summary of Vital Signs and Change from Baseline by Visit during DBTP and Safety Follow-up period - Safety Set		x	x
Table	14.3.4.2.2	Vital Signs - Shift Table of vital signs abnormalities versus Baseline Visit during DBTP and Safety Follow-up period – Safety Set		x	x
ECG					
Table	14.3.4.3.1	Summary of ECG and Change from Baseline by Visit during DBTP - Safety Set		x	x
Table	14.3.4.3.3	ECG - Shift Table of abnormalities versus Baseline during DBTP - Safety Set		x	x

Table	14.3.4.3.4	ECG - Shift Tables of QTC Abnormalities versus Baseline – Safety Set		x	x
Table	14.3.4.3.5	ECG - Proportions of QTC Change abnormalities by Categories and by Visit during DBTP - Safety Set			x
OTHER SAFETY					
Table	14.3.4.4.1	Number of Participants with Suicidal Ideation during DBTP - Safety Set		x	x

9.2.2 Listings

Table 25 List of Listings

	NUMBER	TITLE	Interim Analysis 1 (cohort 1)	Interim Analysis 2 (cohort 1 + cohort 2)	Final analysis (cohort 1 + cohort 2)
TREATMENT ALLOCATION					
Listing	16.1.7.1	Allocation Treatment and IVIg Dose Frequency Stratification Factor - Safety Set	x		x
DISPOSITION					
Listing	16.2.1.2	Participant Disposition and Study Termination - Safety Set	x		x
Listing	16.2.1.4	Analysis Sets - Enrolled Set	x		x
PROTOCOL DEVIATIONS					
Listing	16.2.2.1	Protocol Deviation - Safety Set	x		x
Listing	16.2.2.2	Inclusion Criteria Not Met - Enrolled Set	x		x
Listing	16.2.2.3	Exclusion Criteria Met - Enrolled Set	x		x
PARTICIPANTS EXCLUDED FROM THE EFFICACY ANALYSIS					
Listing	16.2.3.1	Non randomized Participants (ENR minus SAF)			x
DEMOGRAPHICS					
Listing	16.2.4.1	Demographic and Baseline Information - Safety Set	x		x
Listing	16.2.4.2	Medical History - Safety Set	x		x

Listing	16.2.4.3	MMN disease history - Safety Set	x		x
Listing	16.2.4.4	IVIg history - Safety Set	x		x
Listing	16.2.4.5	IVIg treatment during IVDP and IVMP - Safety Set	x		x
Listing	16.2.4.6	Prior Medications - Safety Set	x		x
Listing	16.2.4.7	Prior Procedures - Safety Set	x		x
Listing	16.2.4.8	Concomitant Medications - Safety Set	x		x
Listing	16.2.4.9	Concomitant Procedures - Safety Set	x		x
EXPOSURE AND COMPLIANCE					
Listing	16.2.5.1	Detailed IMP Exposure by Visit - Safety Set	x		x
Listing	16.2.5.2	Overall IMP Exposure by Participant during DBTP - Safety Set	x		x
EFFICACY					
Listing	16.2.6.1.1	Time to Retreatment with IVIg - Safety Set	x		x
Listing	16.2.6.1.2	Time to relapse - Safety Set	x		x
Listing	16.2.6.1.3	Detailed IVIg Exposure during DBTP - Safety Set	x		x
Listing	16.2.6.1.4	Overall IVIg Exposure during DBTP - Safety Set	x		x
Listing	16.2.6.1.5	mMRC-10 and mMRC-14 Sum Scores assessments - Safety Set	x		x
Listing	16.2.6.1.6	GS Daily Average assessments at Visits - Safety Set	x		x
Listing	16.2.6.1.7	GS 3 Day Moving Average - Safety Set	x		x
Listing	16.2.6.1.8	MMN-RODS assessments - Safety Set	x		x
Listing	16.2.6.1.9	9-HPT assessments - Safety Set	x		x

Listing	16.2.6.1.10	EQ-5D-5L assessments - Safety Set	x		x
Listing	16.2.6.1.11	CAP-PRI assessments - Safety Set	x		x
Listing	16.2.6.1.12	PGIC assessments - Safety Set	x		x
Listing	16.2.6.1.13	FSS assessments - Safety Set	x		x
Listing	16.2.6.1.14	HRPQ assessments - Safety Set	x		x
Listing	16.2.6.1.15	TSQM-14 assessments - Safety Set	x		x
PHARMACODYNAMICS					
Listing	16.2.6.3.1	Pharmacodynamics: Free C2, Total C2 and CH50 data - PD Set		x	x
IMMUNOGENICITY					
Listing	16.2.6.4.1	Immunogenicity data: ADA against ARGX-117 - Safety Set			x
[redacted]					
ADVERSE EVENTS					
Listing	16.2.6.7.1	All Adverse Events by Participant and by MedDRA SOC / PT and Verbatim SOC / PT - Safety Set	x		x
Listing	16.2.6.7.2	Serious Treatment Emergent Adverse Events by Participant and by MedDRA SOC/ PT and Verbatim Term - Safety Set	x		x
Listing	16.2.6.7.3	Treatment-Emergent Adverse Events Leading to Withdrawal of IMP by Participant and MedDRA SOC/ PT and Verbatim - Safety Set	x		x

Listing	16.2.6.7.4	Treatment-Emergent Adverse Events Leading to Interruption of IMP by Participant and MedDRA SOC/ PT and Verbatim - Safety Set			x
Listing	16.2.6.7.5	Treatment-Emergent Adverse Events of Special Interest by Participant and by MedDRA SOC / PT and Verbatim - Safety Set	x		x
Listing	16.2.6.7.6	Treatment-Emergent Adverse Events Leading to Death by Participant and by MedDRA SOC / PT and Verbatim-safety Set	x		x
LABORATORY					
Listing	16.2.8.1.1	Laboratory Results: Blood Chemistry Results for Participants with Post-Baseline Abnormalities or Toxicity Grade ≥ 1 - Safety Set	x		x
Listing	16.2.8.1.2	Laboratory Results: Hematology Results for Participants with Post-Baseline Abnormalities or Toxicity Grade ≥ 1 - Safety Set	x		x
Listing	16.2.8.1.3	Laboratory Results: Coagulation Results for Participants with Post-Baseline Abnormalities or Toxicity Grade ≥ 1 - Safety Set	x		x
Listing	16.2.8.1.4	Laboratory Results: Urinalysis Results Postbaseline Abnormalities - Safety Set	x		x
Listing	16.2.8.1.5	Laboratory Results: Antinuclear Antibodies (ANA) and ENA autoantibodies - Results with ANA titer > 1:80 - Safety Set	x		x
Listing	16.2.8.1.6	Laboratory Results for participants entering into the Safety Follow- up period – Safety Set			
VITAL SIGNS					

Listing	16.2.8.2.1	Vital Signs Results for Participants with Post-Baseline Abnormalities - Safety Set	x		x
ECG					
Listing	16.2.8.3.1	12-lead ECG for Participants with Post-Baseline Abnormalities - ECG parameters - Safety Set	x		x
OTHER					
Listing	16.2.8.4.1	Suicidal Ideation for Participants with Abnormal Values [1] - Safety Set	x		x

9.3 eCOA

Table 26 **Derived Variables by eCOA**

Assessment	Endpoint	Derived in eCOA platform (Yes/No)	Derived in ADaM (Yes/No)
mMRC	mMRC-10 sum score	Yes	Yes
	Baseline mMRC-10 Sum Score	Yes	Yes
	mMRC-10 score decrease of at least 2 points compared to baseline	Yes	Yes
	mMRC-14 sum score	Yes	Yes
GS for each hand (most affected and less affected)	GS daily average	Yes	Yes
	GS 3 day moving average	Yes	Yes
	Baseline GS 3 day moving average	Yes	Yes
	% change from DBTP baseline on the GS 3 day moving average	Yes	Yes
	> 30% decrease met on the GS 3 day moving average compared to baseline	Yes	Yes
FSS	FSS total score	Yes	Yes
CAP-PRI	CAP-PRI total score	Yes	Yes

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9.5 [redacted]

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9.6 Laboratory Conversion Factors

Table 28 Laboratory Conversion Factors

Parameter	Original unit	Standard unit	Conversion factor
Bilirubin	mg/dL	µmol/L	17.1
C-Reactive Protein	mg/dL	mg/L	10
Calcium	mg/dL	mmol/L	0.2495
Complement C3	mg/dL	g/L	0.01
Complement C4	mg/dL	g/L	0.01
Creatinine	mg/dL	µmol/L	88.4
Direct Bilirubin	mg/dL	µmol/L	17.1
Glucose	mg/dL	mmol/L	0.05551
Hematocrit	%	Ratio	0.01
Hemoglobin	g/dL	g/L	10
Immunoglobulin G	mg/dL	g/L	0.01
Protein	g/dL	g/L	10
Urea Nitrogen	mg/dL	mmol/L	0.3571

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