TITLE PAGE

Protocol Title:	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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Protocol Version:	4.0
Amendment Number:	3
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Study Phase:	2
Acronym:	ARDA
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Approval Date:	02 Mar 2023

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SPONSOR SIGNATORY

See appended signature page

[redacted], MD, PhD

Chief Medical Officer, argenx BV

Date

INVESTIGATOR'S ACKNOWLEDGMENT

I have read this protocol for study ARGX-117-2002.

Title: 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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	
Signature	
Date	

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document history	Date
Amendment 3 v4.0	02 Mar 2023
Amendment 2 v3.0	12 Dec 2022
Amendment 1 v2.0	16 Feb 2022
Original 1.0	31 Aug 2021

Amendment 3 (02 Mar 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 2 §2 (13) of the Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol was amended to implement an alternative dosing strategy for cohort 2. An option for the dose regimen in cohort 2 was added in case [redacted] are considered for further investigation. Significant changes between protocol version 3.0 and version 4.0 are summarized in the following table. A strikethrough indicates deleted text, and bold font indicates added text. Administrative and editorial changes (eg, to improve readability) are not presented. Refer to Section 10.6 for any undefined abbreviations.

Section and name	Description of change	Brief rationale
2.3.1, Risk Assessment	Table 7, Potential Risks and Mitigation Strategies, was added.	Updated to align with the current IB.
8.3.7, Adverse Events of Clinical Interest	Section added on AEs of Clinical Interest.	Added to align with the current protocol template for ARGX-117 studies and newly added Table 7.
4.3, Justification for Dose 2, Introduction 6.1, Study Intervention(s) Administered, Tables 7 and 8 10.1.5.3, Executive Data Review Team	Added 3 dose regimen options for cohort 2. [redacted]	Based on the totality of the data set in cohort 1 (ie, “snapshot 2 data”), the EDRT has the option [redacted]. [redacted].

Section and name	Description of change	Brief rationale
	[redacted]	[redacted]
4.1.4, Double-Blinded Treatment Period 1.1, Synopsis	Refined randomization details for cohorts 1 and 2, including addition of Figure 2.	Language added because of the dose regimen optionality implemented in cohort 2.
4.2, Scientific Rationale for Study Design 1.1, Synopsis 1.2, Schema 4.3, Justification for Dose 6.3, Measures to Minimize Bias: Randomization and Blinding	Updated language to reflect that the EDRT [redacted]	[redacted]
1.3, Schedule of Activities, Table 1	Footnote (s) updated: ~~A research sample must be collected both before and immediately after the end of the IVIg administration. Research sample collection is optional if the participant receives IVIg at home.~~ **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.**	Clarified that sample collection is at the end of the infusion on the last day, if IVIg is given over several days.
1.3, Schedule of Activities, Table 2	New footnote (o) added: **Sample collection is optional.**	Clarified the requirement of pharmacogenetic sampling in the study.
6.3, Measures to Minimize Bias: Randomization and Blinding 4.1.4, Double-Blinded Treatment Period	Details added on maintenance of blinding throughout cohort 2.	In cohort 2, the participant and the site (except the pharmacist) will remain blinded.
1.3, Schedule of Activities, Tables 1, 2, and 3	ANA titer reporting updated to ≥1:100	Due to a change in the instrument for measuring the ANA and SLE panel

Section and name	Description of change	Brief rationale
8.2.4, Clinical Safety Laboratory Tests 10.2, Appendix 2: Clinical Laboratory Tests, Table 13		at the central laboratory, the new threshold for the smallest titer was implemented to reflect how results are being reported.
8.3.5, Pregnancy	Updated pregnancy follow-up and SAE reporting language, and clarified that any female who becomes pregnant while participating in the trial will discontinue IMP.	Language updated to align with concurrent studies (ARGX-117-2002 and ARGX-117-2003).
9.3.1, General Considerations	Added details for the interim analyses after the completion of cohort 1 and cohort 2.	Language updated to clarify the timing of the interim analyses.
9.3.1, General Considerations 1.1, Synopsis	Language added to specify when final database lock will occur.	Updated to include missing information.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Brief Title:

A clinical trial to investigate the safety and tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of 2 dose regimens of ARGX-117 in adults with multifocal motor neuropathy

Rationale:

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. MMN is considered a chronic immune-mediated neuropathy driven by the classical complement pathway related to the presence of anti-ganglioside GM1 (monosialotetrahexosylganglioside [anti-GM1]) (and other gangliosides) immunoglobulin M (IgM) antibodies produced by a limited number of B cell clones. These antibodies activate the complement system's classical pathway and subsequently yield membrane attack complex (MAC) deposition leading to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and disturbance of membrane integrity at the (para)nodal regions that result in demyelination and motor nerve conduction block.

Patients with MMN initially respond to the standard of care, intravenous immunoglobulin (IVIg); however, the disease will continue to progress despite treatment. There is an unmet medical need for an efficacious treatment option with a more favorable safety and tolerability profile and a shorter duration of administration than the current standard of care.

ARGX-117, a therapeutic complement-inhibiting antibody that targets complement factor 2 (C2), is being developed to reduce tissue inflammation and attenuate the adaptive immune response by blocking both the lectin and classical complement pathways. Inhibition of C2 in complement-mediated neuronal damage is a promising mechanism for preventing axonal and glial injury. In an ex vivo mouse model of acute neuropathy, the use of a C2 blocking antibody (Bro2) in *GalNAcT*$^{-/-}$*-Tg* (*neuronal*) mice prevented the loss of neurofilament staining at the nerve terminal, thereby maintaining axonal integrity. Additionally, C2 inhibition by Bro2 in *GalNAcT*$^{-/-}$*-Tg(glial)* mice resulted in the preservation of ankyrin B at the distal paranode. Using an in vitro model for MMN, ARGX-117 blocked IgM-mediated classical pathway complement activation on both motor neurons and Schwann cells, providing further support for developing ARGX-117 in patients with MMN.

The safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of single and multiple doses of ARGX-117 administered intravenously (IV), and ARGX-117 comixed with recombinant human hyaluronidase PH20 (rHuPH20) administered

subcutaneously (SC), are being evaluated in the ongoing, first-in-human (FIH), phase 1 study, ARGX-117-1901.

This phase 2 clinical trial serves to evaluate the safety and efficacy of different dose regimens of ARGX-117 versus placebo, in participants with MMN previously stabilized with IVIg.

Study Design:

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 different dose regimens of ARGX-117 in adults with MMN. Two cohorts of at least 24 participants each are planned for enrollment.

This trial consists of a screening period, an IVIg dependency period (if applicable), an IVIg monitoring period, a double-blinded treatment period (DBTP), and a safety follow-up period.

All participants will begin with a screening period and the diagnosis of MMN will be assessed by the MMN Confirmation Committee (MCC). The MCC will also assess IVIg dependency. Participants whose IVIg dependency is uncertain will enter an IVIg dependency period to assess the impact of a delayed IVIg administration on grip strength (GS) and/or motor function. The IVIg criterion is considered fulfilled in an individual stabilized to IVIg for longer than 3 months if a clinically meaningful deterioration from any of these 2 parameters is established. The IVIg criterion is also considered fulfilled if an individual stabilized to IVIg for less than 3 months demonstrates a clinical improvement following the initiation of IVIg therapy.

After completing the screening period (including the IVIg dependency period, if applicable), all participants will begin the IVIg monitoring period. Participants will receive IVIg during the IVIg monitoring period at a frequency, duration, and dose established by their medical history. The IVIg monitoring period includes 3 IVIg treatment cycles and will establish baseline values for all clinical endpoints assessed during the DBTP.

Participants will be randomized on day 1 of the DBTP (Refer to Section 6.1):

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

Randomization will be stratified based on an individual's IVIg dose frequency:

1. IVIg dosed every 2 or 3 weeks
2. IVIg dosed every 4 or 5 weeks

The dosing of ARGX-117 or placebo will begin on day 1 of the DBTP, 7 days after the final IVIg administration of the IVIg monitoring period.

Participants will be retreated with IVIg during the DBTP if there is a clinically meaningful deterioration in muscle strength and/or motor function. Investigational medicinal product (IMP) administration will continue throughout the DBTP. A clinically meaningful deterioration is defined as a >30% decline in the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the modified Medical Research Council (mMRC)-10 sum score. Based on their clinical judgment, the

investigator may choose to not re-treat the participant with IVIg. All trial participants can request IVIg retreatment anytime during the DBTP.

End of Trial/Rollover

After completing the 16-week DBTP, participants may enroll in a long-term extension (LTE) study and receive ARGX-117; otherwise, participants will enter the 15-month safety follow-up period (Table 3 Section 1.3).

[redacted]

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

Number of Participants

At least 48 participants are planned to be randomized to the DBTP (Section 9.4).

At least 24 participants will be included in cohort 1

- 16 participants to ARGX-117 dose regimen 1
- 8 participants to placebo

At least 24 participants will be included in cohort 2, according to one of the following options selected by the EDRT (Section 10.1.5.3):

[redacted]

If additional participants are screened and eligible for enrollment in cohort 2 before a decision is made to open cohort 2, those participants will be assigned to cohort 1.

Intervention Groups and Duration

The first IMP administration will begin 7 days after the final IVIg administration at the end of the IVIg monitoring period.

IMP includes:

- ARGX-117 administered by IV infusion
- Placebo administered by IV infusion

ARGX-117 and placebo will be administered by an IV infusion over approximately 2 hours at visit 1. ARGX-117 and placebo will be administered by an IV infusion over approximately 1 hour for all subsequent administrations.

Dose regimen 1 will be assessed in cohort 1. Dose regimen 1 will include [redacted] mg/kg ARGX-117 or placebo [redacted]

Three options are available as the dose regimen for cohort 2, of which **1** will be assessed per the decision of the EDRT:

- [redacted]
- [redacted]
- [redacted]

MMN Confirmation Committee

The investigator's diagnosis of MMN will be reviewed by the MCC during the screening period. The MCC will ensure that the trial population fulfills the criteria for probable or definite MMN according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 guidelines. Individuals for whom the diagnosis cannot be confirmed will be ineligible for this trial.

The MCC will also assess the IVIg dependency criterion. If IVIg dependency is uncertain, the participant will enter an additional period to assess dependency following a delayed administration of IVIg and continue into a subsequent IVIg monitoring period once the IVIg dependency criterion has been fulfilled.

The MCC will be composed of neurologists with expertise in the diagnosis and treatment of MMN. A trial participant profile will be developed and presented for MCC review, as described in the MCC charter. All trial sites will be trained and instructed on the MCC review process.

Independent Data Monitoring Committee

The independent data monitoring committee (IDMC) will monitor accumulating safety data. Committee composition will depend on the scientific skills and knowledge required for trial monitoring and will include at least 3 independent members, including a statistician.

The IDMC will review and evaluate safety data and make recommendations on continued dosing within a cohort, the opening of cohort 2, and modification or discontinuation of the trial. [redacted]

- [redacted]
- [redacted]
- [redacted]

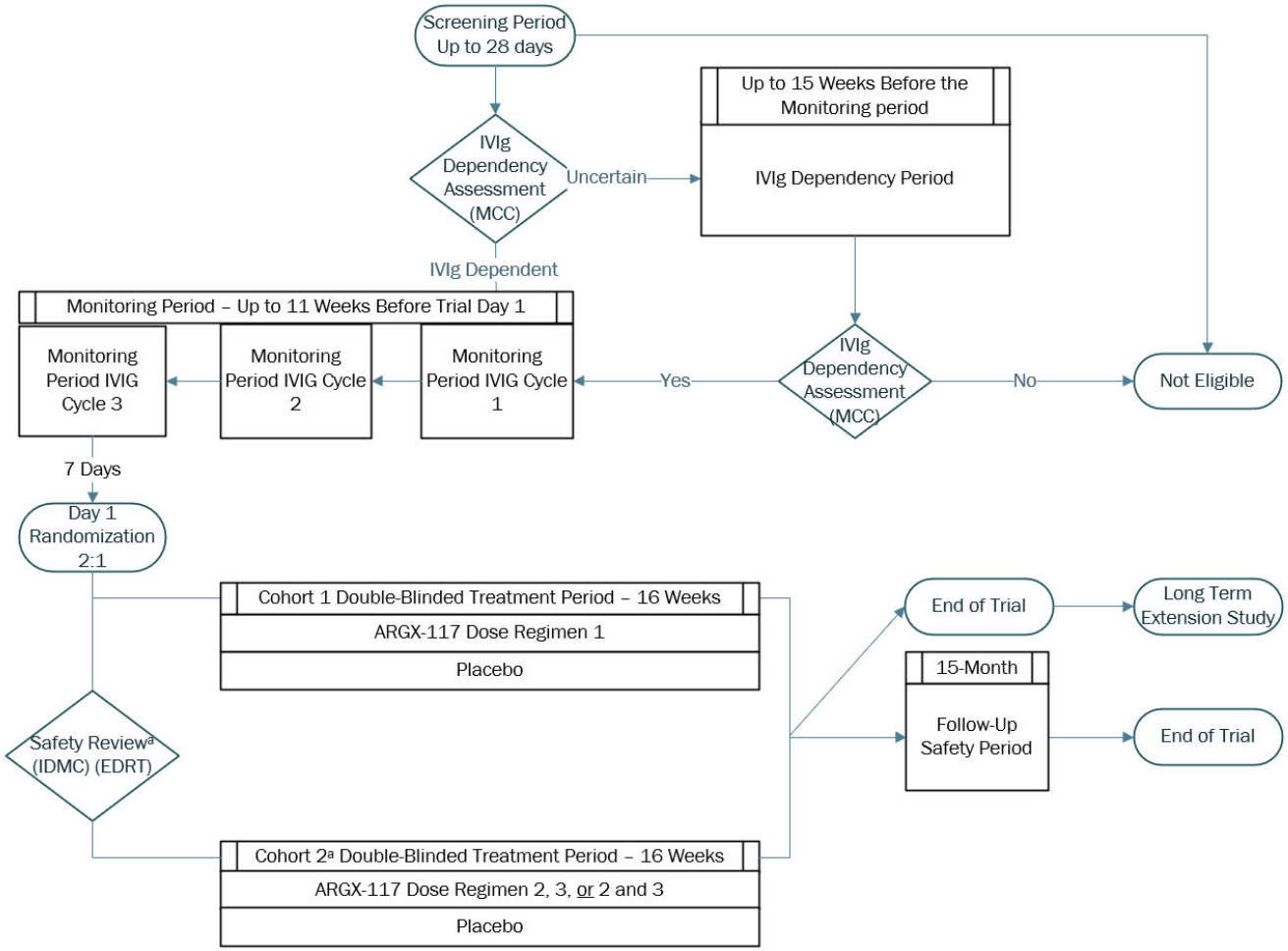
The roles and responsibilities of the IDMC will be described in the IDMC/ unblinded executive data review team (EDRT) charter.

Unblinded Executive Data Review Team

An EDRT will be established for the strategic development of ARGX-117, including, but not limited to, the decision to open cohort 2, and if applicable, the selection of the final dose regimen option, following recommendations from the IDMC. The EDRT will have access to unblinded trial information that will remain confidential to the EDRT and will not be communicated to the blinded trial team, site staff, or participants, to mitigate the risk of releasing treatment assignment to sites and participants.

The roles and responsibilities of the EDRT will be described in the IDMC/EDRT charter.

1.2. Schema



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]

1.3. Schedule of Activities

Table 1: 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[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							
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[g]		X			X		
FSH level[h]		X					
Physical examination[i]		X	X	X	X	X	X
Vital sign measurements[j]		X	X	X	X	X	X
12-lead ECG(s)[k]		X				X	X
SIB risk and monitoring[l]		X	X	X	X	X	X
Samples for safety laboratory tests		X	X	X	X	X	X
Samples for SLE panel[m]		X					
Samples for urinalysis		X					X

Table 1: IVIg Dependency and IVIg Monitoring Period Schedule of Activities Through Day −7 (Continued)

	IVIg Dosing Frequency	SCN[a]	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[n]			X	X	X	X	X
Samples for immunogenicity[o]		X					
[redacted]							
Virology screen		X					
Pharmacogenetic sample		X[q]					
[redacted]							
[redacted]							
Research sample[r]					X[s]	X[s]	X[s]
IVIg administration[t]			X	X	X	X	X
Grip strength[u]		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
14-item TSQM					X	X	X

Table 1: IVIg Dependency and IVIg Monitoring Period Schedule of Activities Through Day −7 (Continued)

	IVIg Dosing Frequency	SCN[a]	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							
Concomitant medication/procedures[v]		Continuous monitoring					
Adverse events[v]		Continuous monitoring					

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. Refer to Section 2.3.3 for more details.

[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. Further information is provided in Section 4.1.2 and Figure 1.

[c] The IVMP occurs up to 11 weeks before day 1 of the DBTP. The IVMP is further described in Section 4.1.3.

[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.
[j] Vital signs will include the measurements described in Section 8.2.2. 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 (Table 2).
[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 timepoints. See Section 8.2.3.
[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 as described in Section 8.2.6 .
[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. Further information is provided in Section 8.5.
[o] Immunogenicity assessments will be performed predose of IVIg administration. See Section 8.9 for more details
[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 trial visits and monitored daily starting from the IVDP or IVMP (Section 8.1.1.3).
[v] 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.

Table 2: IMP Administration Period Schedule of Activities, [redacted]

[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)
Pregnancy test[e]	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)
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)

[redacted]																
Activity																
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]																
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]

Activity																
[redacted]																
Grip strength[s]	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)
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/ procedures[t]	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. Refer to Section 2.3.3 for more details.

[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 (Section 8.1.1.1). 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 done for the participant to receive IVIg. Further details are provided in Section 6.7.

[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 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.

[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 timepoints. See Section 8.2.3.

[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 as described in Section 8.2.6.

[j] An ANA test will be performed at the specified timepoints, 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] [redacted]

[m] Immunogenicity assessments will be performed predose of IMP administration. See Section 8.9 for more details.

[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 as described in Section 6.7.

[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. Further information on study interventions and IMP are provided in Section 6 and Section 7. Details regarding temporary discontinuation of IMP are provided in Section 7.2.1.

[s] Grip strength will be measured on-site at all visits and monitored daily (Section 8.1.1.3).

[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 3: Follow-up Period Schedule of Activities

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]

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. Refer to Section 2.3.3 for more details.

[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.

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

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

[e] An ANA test will be performed at the specified timepoints, 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.

[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 4: Blood Collection Schedule for PK and PD Analyses [redacted]

[redacted]

Table 5: Blood Collection Schedule for PK and PD Analyses [redacted]

[redacted]

Table 6: [redacted]

[redacted]

[redacted]

2. INTRODUCTION

ARGX-117 is a humanized recycling antibody that binds specifically to the C2b part of C2 in a pH- and Ca2+- dependent manner. Binding of ARGX-117 inhibits the function of C2 and blocks downstream complement activation.

ARGX-117 is being developed to reduce tissue inflammation and attenuate the adaptive immune response by blocking complement activity. The safety and tolerability of ARGX-117 administered intravenously (IV) and ARGX-117 comixed with recombinant human hyaluronidase PH20 (rHuPH20) administered subcutaneously (SC) in healthy adult participants compared to placebo is being evaluated in an ongoing phase 1 first-in-human (FIH), randomized, double-blind study (ARGX-117-1901). This single and multiple ascending dose trial is also evaluating the pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of ARGX-117.

Complement-mediated diseases can potentially benefit from ARGX-117 intervention, including MMN, a chronic, immune-mediated neuropathy, characterized by asymmetric predominantly distal weakness of limbs.

ARGX-117-2002 will evaluate the safety and tolerability, efficacy, PK, PD, and immunogenicity of different IV dose regimens of ARGX-117 in adults with multifocal motor neuropathy (MMN).

2.1. Study Rationale

Nonclinical and clinical studies suggest that ARGX-117 administered IV has a favorable safety profile and may be an effective compound in complement-mediated diseases such as MMN. This trial serves to evaluate the safety and tolerability, efficacy, PK, and PD of ARGX-117 in adults with MMN.

2.2. Background Information

MMN is considered a rare chronic immune-mediated neuropathy involving progressive muscle weakness of mainly the hands, forearms, and lower legs. It is clinically characterized by progressive asymmetric weakness involving 2 or more nerves and partial motor conduction block. The estimated prevalence of MMN is between 0.6 to 2 per 100 000 people and typically presents as an asymmetrical upper limb pure motor neuropathy.[1] The hallmark of the disease is the presence of multifocal motor conduction blocks, ie, impaired propagation of action potentials along the axon, and patients often show high serum levels of immunoglobulin M (IgM) antibodies against the ganglioside GM1 (monosialotetrahexosylganglioside). GM1 is widely expressed in the nervous system by neurons, particularly around the node of Ranvier, and Schwann cells.[2,3,4] The current prevailing view is that GM1 antibodies target the axolemma at the node of Ranvier. This is thought to interfere with axon-Schwann cell interactions, causing widening of the node, and direct damage to the axon.[5,6]

The presence and titers of IgM anti-ganglioside GM1 (anti-GM1) antibodies and their complement activating properties, correlate with clinical features such as weakness and axonal damage.[7] Moreover, the binding and subsequent classical complement pathway activation of anti-GM1 IgM from patients with MMN to motor neurons derived from induced pluripotent stem

cells causes disturbed calcium homeostasis and structural damage to these pluripotent cells in vitro, resembling the changes that occur in MMN.[8]

Anti-GM1 (and other gangliosides) IgM antibodies are produced by a limited number of activated B cells; however, the mechanism of this B cell activation has not yet been established. Binding of these anti-GM1 antibodies to GM1 leads to activation of the classical complement pathway, and subsequent MAC deposition. Consequently, this MAC deposition leads to disruption of Schwann cell-axolemma junctions, displacement of ion-channel clustering, and the disturbance of membrane integrity at the (para)nodal regions resulting in demyelination. Anti-GM1 IgM antibodies are identified in at least 40% of patients with MMN.

These findings suggest that complements play an important role in the pathogenesis of MMN, therefore, the inhibition of complement activation may provide a new therapeutic option in this disease.

High dose IV immunoglobulin (IVIg) treatment is the only approved treatment for MMN.[9,10] IVIg treatment often improves muscle strength; however, the efficacy of IVIg in reducing MMN symptoms declines after several years and many patients report progressive neurological deficits.[11,12] The mechanism of action of IVIg in MMN is not well understood; however, IVIg may have effects on humoral immunity beneficial to those with MMN. IVIg partially reduced complement activity in sera[13] and may interfere with anti-GM1 IgM-mediated complement nerve deposition.[13,14] Despite treatment with IVIg, MMN related disabilities will continue to progress due to ongoing axonal degeneration. Complement-modulating treatment was previously evaluated using eculizumab, a monoclonal antibody against complement factor 5 (C5) preventing formation of MAC. Results showed that eculizumab was well tolerated, however, only a small improvement was seen in selected motor performance measurements.[15] Considering the high levels of CD59 expression, iPSC-derived motor neurons show a high innate ability to inhibit the terminal portion of the complement cascade. Thus, the use of a C5 inhibitor to preserve motor neuron function may be limited. Moreover, C5 is downstream of C3, whereas the presence of C3aR on MNs suggest that complement activation upstream of C5 may have functional consequences for MNs.

There is an unmet medical need for an efficacious treatment option with a more favorable safety and tolerability profile and shorter duration of administration than the current standard of care.

2.2.1. Nonclinical

2.2.1.1. Nonclinical Pharmacology

[redacted]

[redacted]

2.2.1.2. Pharmacokinetics and Pharmacodynamics

[redacted]

2.2.1.3. Nonclinical Toxicology

[redacted]

[redacted]

2.2.2. Clinical

Refer to the current ARGX-117 IB for information on the PK, PD, and safety of ARGX-117.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

ARGX-117 specifically binds C2 and therefore inhibits both the classical and lectin pathways but not the alternative pathway. The human safety risk from off-target effects of monoclonal antibody therapeutics is generally considered to be low as no off-target binding was observed in preclinical studies. The risks associated with short-term inhibition of the complement system also appear to be low based on the available information for several approved products in this therapeutic class (eg, Soliris, Berinert, Cinryze, Ruconest, and Cetor).

The risks associated with the long-term inhibition of the proximal portion of the classical and lectin pathways of the complement system are currently unknown. The complement system plays an important role in protection against encapsulated bacteria including Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae.[16] Participants are therefore required to be immunized against these bacteria as a prerequisite to participating in the trial to mitigate the risk of infection (Section 5.1).

Chronic inhibition of C2 could potentially decrease the ability of the immune system to clear immune complexes, which could lead to an increased risk of systemic lupus erythematosus (SLE). Samples will be taken to test for a panel of lupus-associated autoantibodies throughout the trial as described in the SoA (Section 1.3).

Adults included in this trial were previously stabilized to IVIg to control their MMN and will be at risk for a temporary resurgence of MMN symptoms during the double-blinded treatment period (DBTP) due to the following:

- The IVIg withdrawal design
- Clinical efficacy of ARGX-117 has not been established
- 1 of 3 participants will be randomized to placebo

The risk of clinical deterioration will be limited to predefined thresholds at which participants will be re-treated with IVIg (Section 4).

As with any IV infusion, the potential exists for infusion-related reactions to occur during or within 48 hours following the administration of ARGX-117. Participants will be monitored at the clinic for at least 1 hour after IMP administration.

Refer to the current ARGX-117 IB for information on the safety of ARGX-117.

Table 7: Potential Risks and Mitigation Strategies

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Systemic lupus erythematosus	Chronic inhibition of C2 could potentially decrease the ability of the immune system to clear immune complexes, which could lead to an increased risk of systemic lupus erythematosus.	Samples will be collected to test for a panel of lupus-associated autoantibodies, as described in the SoA (Section 1.3).
Encapsulated bacterial infection	The complement system plays an important role in protecting against encapsulated bacteria, including *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.	Immunize participants against these bacteria before the study.
Hypersensitivity and local administration site reactions	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. As with any SC or IV injection, injection- or infusion-related reactions can occur during or after administration.	Continuously monitor participants for hypersensitivity and local administration site reactions. Hypersensitivity and local administration site reactions are considered AEs of clinical interest (Section 8.3.7).

AE=adverse event; C2=complement component 2 protein; IV=intravenously; SC=subcutaneously; SoA=schedule of activities

2.3.2. Benefit Assessment

Clinical proof of efficacy for ARGX-117 has not been established in MMN. Complement inhibition by ARGX-117 is expected to mitigate the symptoms of MMN and reduce the need for IVIg treatment and its associated treatment burden.

Results from this trial will contribute to the understanding of the impact of complement inhibition on MMN.

2.3.3. COVID-19

As a result of COVID-19, the sponsor has considered changes in the conduct of the trial that may be necessary to protect the safety of the participants and the site staff.

During the trial, the sites will implement all local recommendations regarding the spread of COVID-19, including specific guidelines related to clinical research performed in clinical research centers.

Participants are not tested for SARS-CoV-2 as part of this trial, except for Germany, as specified in Section 1.3. All participants with clinically significant uncontrolled infections, malignancies,

or recent surgeries are excluded (refer to Section 5.2). Contact the medical monitor if a participant tests positive for SARS-CoV-2 at any point.

Additional testing for COVID-19 is not required during the trial. However, it is recommended that participants who develop COVID-19 symptoms be tested and results reported for the trial.

2.3.4. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to participants in this trial, the potential risks identified in association with ARGX-117 are justified by the anticipated benefits that may be afforded to participants with MMN.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of ARGX-117 can be found in the IB and participant information leaflet.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of ARGX-117 compared to placebo in adult participants previously stabilized with IVIg	• Safety outcomes based on adverse event (AE) monitoring and other safety assessments
Secondary	
• To evaluate the efficacy of ARGX-117 compared to placebo on muscle strength and/or motor function in adult participants previously stabilized with IVIg	• Time to the first retreatment with IVIg[a] since the final IVIg treatment of the IVIg monitoring period • Time-to-relapse **modified Medical Research Council (mMRC)** • AUC of the change from baseline in mMRC-10 sum score • Value and change from baseline in the average score of the 2 most important muscle groups as assessed by the mMRC-14 sum score • Value and change from baseline in the mMRC-14 sum score • 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 **Grip strength (GS)** • AUC of the change from baseline in GS • Proportion of participants with a GS decrease of 8 kilopascal (kPa) or more over 3 consecutive days

	• Values, change, and percent change from baseline in GS
• To evaluate the efficacy of ARGX-117 on functional ability, arm and hand function, quality of life, and fatigue in adult participants with MMN	• Values and change from baseline in the Rasch-built overall disability scale for MMN (MMN-RODS©) • Values and change from baseline in the average time for the upper extremity (arm and hand) function (9 Hole Peg Test [9-HPT], or timed pegboard test) • Proportion of participants by level of severity on each dimension of the EQ-5D-5L scale • Value and change from baseline in EQ-5D-5L visual analog scale (VAS) • Values and change from baseline in the chronic acquired polyneuropathy patient-reported index (CAP-PRI) • Values of the Patient Global Impression Change (PGIC) scale • Values and change from baseline in the 9-item Fatigue Severity Scale (FSS)
• To evaluate the effect of ARGX-117 on health-related productivity and work productivity	• Values for work-related and household chore activities of the Health-Related Productivity Questionnaire (HRPQ) at each visit: – Hours lost because of absenteeism – Hours lost because of presenteeism – Total hours lost (absenteeism + presenteeism) – Percentage of scheduled hours lost because of absenteeism – Percentage of scheduled hours lost because of presenteeism – Percentage of scheduled hours lost in total (absenteeism + presenteeism)
• To evaluate medication treatment satisfaction	• Effectiveness, side effects, convenience, and overall satisfaction scores as assessed by the Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM)

• To assess the PK, PD, and immunogenicity of ARGX-117	• Serum concentrations and PK parameters for ARGX-117 • Values and change from baseline in free C2, total C2, functional complement activity (CH50) • Incidence and prevalence of ADA against ARGX-117
Exploratory	
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[a] [redacted].

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2, randomized, stratified, double-blinded, placebo-controlled, parallel-group, multicenter trial of ARGX-117 in adults with MMN.

The total trial duration is at minimum 25 weeks for all participants. The order and duration of study periods is as follows for both cohort 1 and cohort 2:

- Screening period: Up to 28 days (Table 1 Section 1.3)
- IVIg dependency period (IVDP) (if applicable) (Table 1 Section 1.3): Only participants whose IVIg dependency is uncertain at the end of the screening period will enter the IVDP. See Section 4.1.2 for further details on the IVDP
- IVIg monitoring period (IVMP) (Table 1 Section 1.3): The length of the IVMP will depend on the participant's IVIg dose frequency. See Section 4.1.3
- DBTP (Table 2 Section 1.3): 16 weeks (Section 4.1.4)
- Safety follow-up period (Table 3, Section 1.3): Participants who do not enroll into the long-term extension study (LTE) (Section 6.5) will enter the 15-month safety follow-up period after completing the DBTP

Two cohorts are planned for enrollment. [redacted] The IDMC will make recommendations that will inform the unblinded executive data review team (EDRT) on the decision to begin the enrollment of cohort 2.

The diagnosis of MMN and IVIg dependency will be assessed by the MMN Confirmation Committee (MCC) (Appendix 1, Section 10.1.5.1) during the screening period. Participants whose IVIg dependency is uncertain will enter the IVDP to assess the impact of delayed IVIg administration on grip strength (GS) and/or motor function (Section 4.1.2).

The IDMC will monitor accumulating safety data throughout the trial (Appendix 1, Section 10.1.5.2).

4.1.1. Screening Period

The screening period will be used to determine an individual's eligibility to participate in the trial. Assessments will be taken as described in the SoA, see Table 1 in Section 1.3.

The screening period will occur over 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.

An additional extension of the screening period to align a participant's subsequent IDV1 or IMV1 with their IVIg dosing schedule will not lead to screen failure.

4.1.2. IVIg Dependency Period

The IVDP will be used to determine the IVIg dependency of participants whose IVIg dependency is uncertain based on the description provided to the MCC summarized in the participant profile during screening.

The IVDP will last up to 15 weeks (105 days) depending on the IVIg dose frequency. A participant's IVIg administration will be delayed during the IVDP.

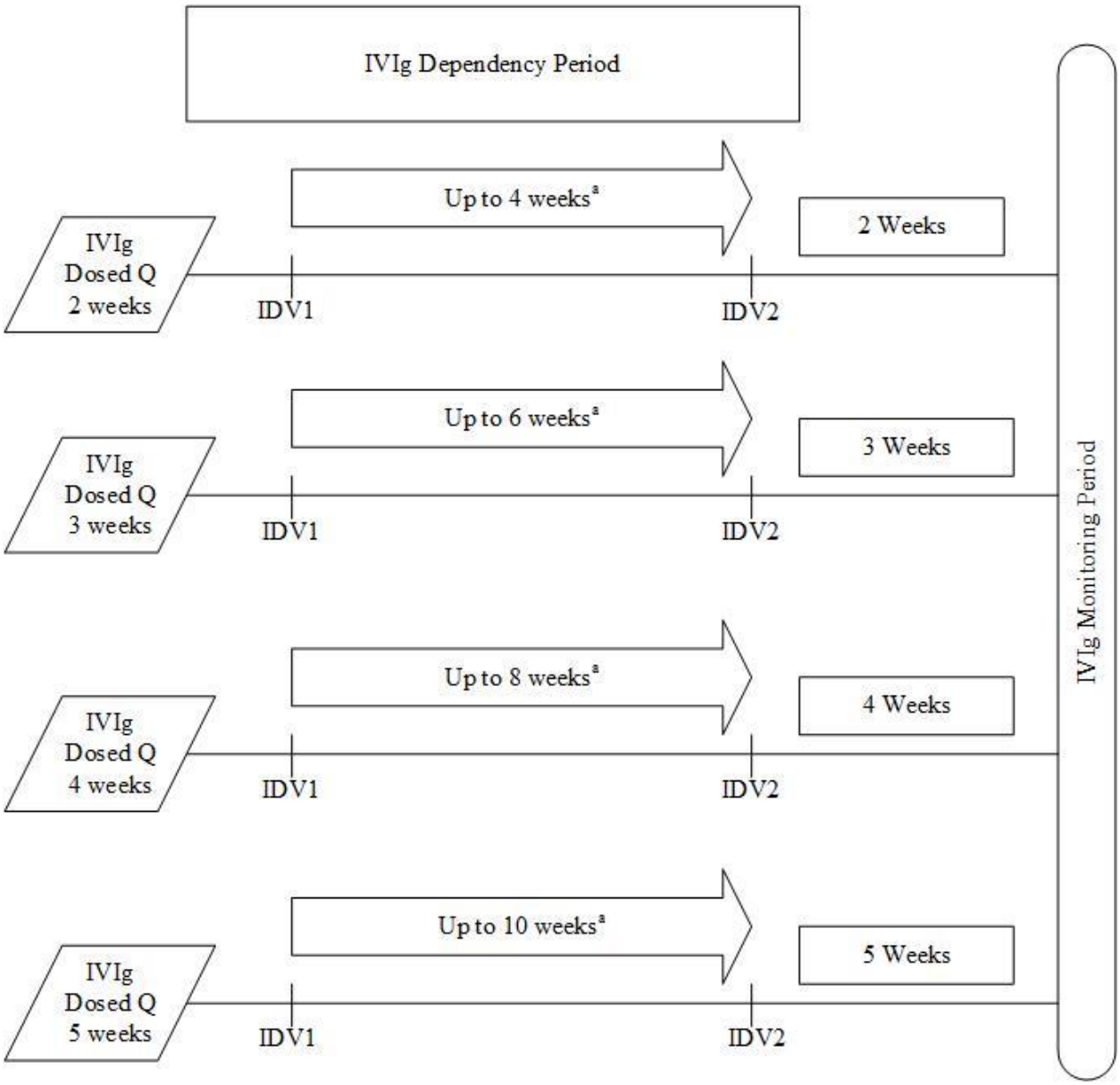
Assessments will be taken at the time points described in the SoA, see Table 1 in Section 1.3. Study assessments and procedures are described in Section 8.

Participants will receive IVIg following a delayed administration compared to their stable IVIg regimen interval. Frequency of visits during the IVDP is provided in Figure 1.

- 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]

Figure 1: IVDP Visit Frequency



IDV=IVIg dependency period visit; IVIg=intravenous immunoglobulin; Q=every

[a] IDV2 will occur earlier than planned if a participant demonstrates a clinically meaningful deterioration between the scheduled visits.

4.1.3. IVIg Monitoring Period

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 (Table 1 Section 1.3).

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

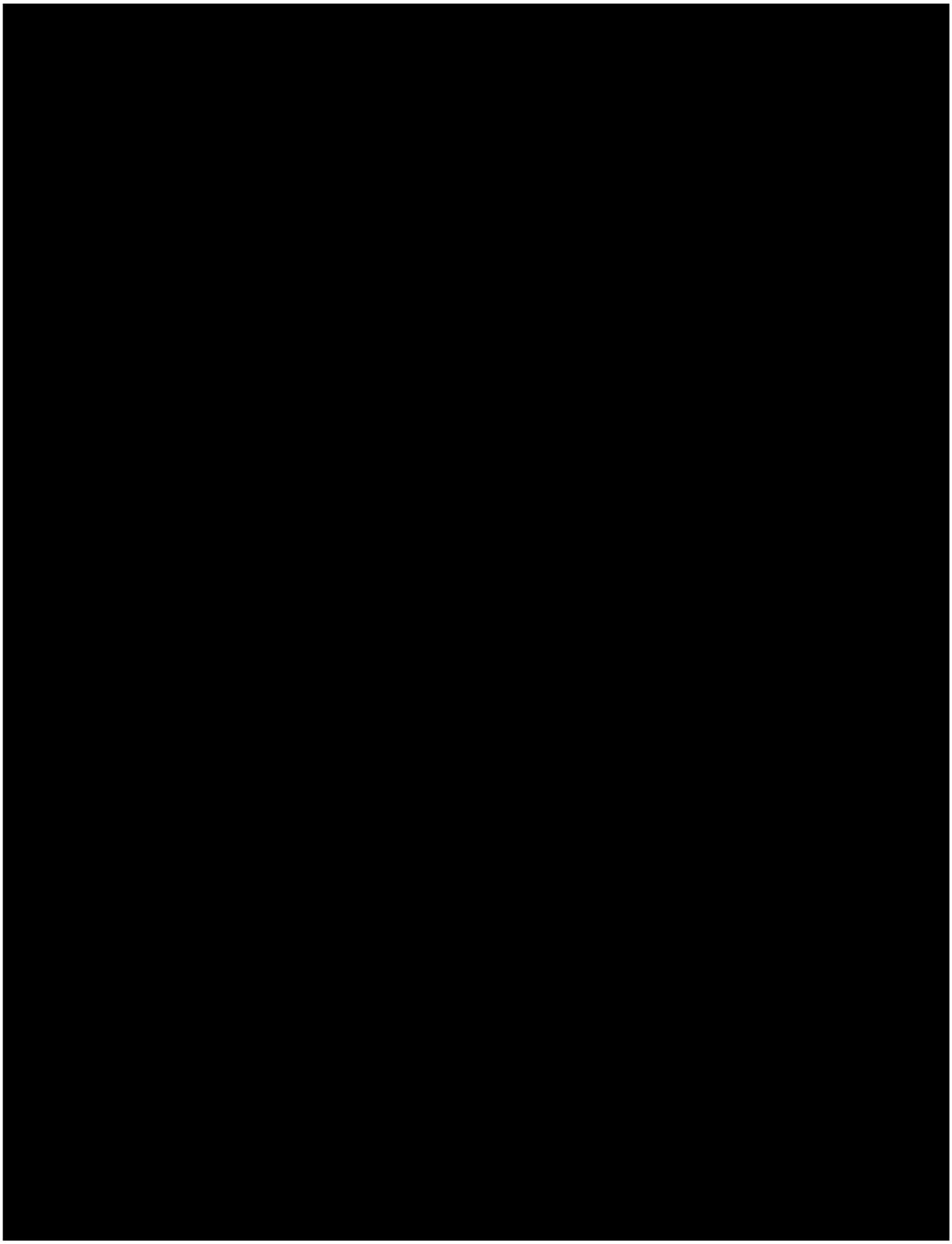
The length of the IVMP may be greater if a participant receives IVIg over the course of several days. Assessments will be done at the time points described in the SoA (Table 1 Section 1.3). Study assessments and procedures are described in Section 8.

4.1.4. Double-Blinded Treatment Period

The dosing of IMP will begin on day 1 and continue throughout the DBTP as described in the SoA (Section 1.3, Table 2).

- The DBTP will begin 7 days after the final IVIg administration of the IVMP (Section 4.1.3).
- Participants will be randomized at day 1 of the DBTP:
  - In a 2:1 ratio to ARGX-117 or placebo in cohort 1, and for option 1 (dose regimen 2[redacted]) or option 2 (dose regimen 3[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 (Figure 2).
  - [redacted]
- 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 assessment.
- Participants will be re-treated with IVIg during the DBTP if there is a clinically meaningful deterioration in muscle strength and/or motor function. A clinically meaningful deterioration is defined as a >30% decline in the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score since randomization.
  - 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 trial participants can request IVIg retreatment with the investigator anytime during the DBTP

Figure 2: [redacted]



4.1.5. Follow-up Period

The safety follow-up period will characterize safety, PK, and PD during the elimination of ARGX-117. The safety follow-up period will begin after the DBTP and will continue over 15 months. Assessments will be done at the time points described in the SoA (Table 3 Section 1.3).

Only participants that do not roll over into the LTE will enter the safety follow-up period.

4.2. Scientific Rationale for Study Design

ARGX-117, a therapeutic complement-inhibiting antibody that targets complement factor 2 (C2), is being developed to reduce tissue inflammation and attenuate the adaptive immune response by blocking both the lectin and classical complement pathways. Inhibition of C2 in complement-mediated neuronal damage is a promising mechanism for preventing axonal and glial injury. In an ex vivo mouse model of acute neuropathy, the use of a C2 blocking antibody (Bro2) in GalNAcT-/--Tg (*neuronal*) mice prevented the loss of neurofilament staining at the nerve terminal, thereby maintaining axonal integrity. Additionally, C2 inhibition by Bro2 in GalNAcT-/--Tg(*glial*) mice resulted in the preservation of ankyrin B at the distal paranode. [17] Using an in vitro model for MMN, ARGX-117 blocked IgM-mediated classical pathway complement activation on both MNs and Schwann cells, providing further support for developing ARGX-117 in patients with MMN.[17]

The randomized IVIg withdrawal design and subsequent retreatment with IVIg due to deterioration in MMN disease activity has been used in previous trials in patients with MMN.[18] This trial design is based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E10 “Choice of Control Group in Clinical Trials” and is able to limit placebo exposure if a poor clinical response is observed. Withholding IVIg from trial participants randomized to the placebo arm is assumed to yield a deterioration in MMN disease activity requiring the restart of IVIg after an estimated mean time of 4 weeks of double-blind treatment for placebo randomized participants whereas for participants randomized to the ARGX-117 arm(s) the trial hypothesis is that the time to IVIg retreatment is at least 4-fold longer.

The inclusion of a placebo group is considered important to the design of ARGX-117-2002 because a placebo arm allows for an accurate assessment of the safety and tolerability, clinical efficacy, PK, PD, and immunogenicity of the study drug. Comparison of ARGX-117 to placebo optimizes the interpretability of safety, tolerability, clinical effects data, PK, PD, and immunogenicity of the study drug.

The criterion for retreatment with IVIg will be based on clinical deterioration, defined as a >30% decline in the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score. Both GS and mMRC-10 sum score are standard and clinically relevant instruments used to measure clinical efficacy in clinical trials in MMN.[18,19] By using these measures as criteria for retreatment with IVIg, the time to retreatment is thus directly related to clinically meaningful outcomes. Both outcomes will be assessed separately as secondary endpoints, to support the results of the time to retreatment with IVIg endpoint. The respective thresholds for deterioration are set to represent clinically significant declines in disease activity.[18,19]

Randomization will be performed 7 days after the last IVIg administration of the IVMP as it is expected that the clinical benefit of the IVIg treatment is optimal at this point in time for both GS and the mMRC sum score. Assessments performed on the day of randomization will be used as reference for assessing clinical deterioration.

Two cohorts will be enrolled in a sequential fashion. Cohort 1 will assess [redacted] and cohort 2 will assess [redacted] depending on the decision from the EDRT. An IDMC will review and evaluate safety data at prespecified time points and make recommendations on continued dosing within a cohort, the opening of cohort 2, and modification or discontinuation of the trial (Appendix 1, Section 10.1.5.2). Given the 3 available options, the EDRT will make the final decision on the dose regimen for cohort 2. The option chosen for cohort 2 will remain blinded to the site, participant, and the study team of the sponsor.

A 16-week DBTP is a sufficient length to assess the safety and tolerability of ARGX-117 and to observe a reduced need for IVIg treatment. ARGX-117 is expected to prolong the need for retreatment with IVIg in comparison to placebo by 4 times (16 weeks compared to 4 weeks).

Participants will enter the safety follow-up period or enroll into an LTE study (ARGX-117-2003) after completion of the DBTP.

Based on the available data, the mean elimination half-life of ARGX-117 ranges from approximately 70 to 88 days for the doses [redacted]. The safety follow-up period will continue for 15 months based on the half-life of ARGX-117. The safety follow-up period is designed to characterize safety, PK, and PD during the elimination of ARGX-117.

4.2.1. Participant Input Into Design

A panel discussion with patients with MMN was organized in Jan 2021 in collaboration with the GBS/CIDP Foundation to discuss the design and feasibility of the trial.

4.3. Justification for Dose

Different dose regimens will be investigated in this trial:

Cohort 1:

Dose regimen 1

[redacted]

Cohort 2:

Three options are available for cohort 2, of which **1** will be selected per the decision of the EDRT (Section 10.1.5.3):

- [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

The relationship between free C2 concentrations and CH50 activity following ARGX-117 administration to healthy participants in study ARGX-117-1901 indicates that a small amount of free C2 is capable of triggering the complement cascade reflected in CH50 activity. Therefore, different free C2 thresholds were selected to target 99%, 98%, or 96% reduction in free C2 levels.

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

4.4. End of Trial Definition

A participant is considered to have completed the trial if he/she has completed any of the following:

- The last visit of the DBTP period and will roll over into the LTE
- The last visit of the follow-up period described in the SoA (Section 1.3)

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:

1. Capable of giving signed informed consent as described in Appendix 1, Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol (including consent for the use and disclosure of research related health information). Participants must be able to read and write and be willing and able to comply with the trial protocol procedures (including attending the required trial visits)
2. Male/female at least 18 years of age at the time the ICF is signed
3. Probable or definite MMN according to the EFNS/PNS 2010 guidelines (Appendix 8, Section 10.8) at screening confirmed by the MCC

4.1. Receiving a stable IVIg regimen for at least 3 months before screening or recently initiated IVIg treatment (refer to inclusion criterion 5.1a), AND both of the following:

a. IVIg treatment interval of 2 to 5 weeks
b. IVIg dose of 0.4 to 2.0 grams per kg body weight and infusion

5.1. IVIg treatment dependency confirmation by the MCC at screening or after IVDP when applicable, based on 1 of the following:

a. Recently initiated IVIg treatment (less than 3 months):

   – Clinical improvement following IVIg initiation documented in the participant's medical record

b. Maintenance therapy with IVIg (longer than 3 months), based on 1 of the following:

   – Clinical deterioration following IVIg withdrawal, IVIg dose reduction, or IVIg delayed administration within 12 months prior to screening (documented in the participant's medical record)

   – Clinical deterioration following IVIg delayed administration during the IVDP

6.2. Immunization with the first meningococcal vaccine and pneumococcal vaccine, and the single Haemophilus influenza type B vaccine must be performed at least 14 days before IMP administration at V1 according to local country-specific immunization schedules. A documented history of vaccination against Neisseria meningitides, Haemophilus influenza type B, and streptococcus pneumonia will be permitted

- **Germany only:** Participants must be fully vaccinated against COVID-19 according to local country-specific immunization schedules if required locally.

7.1. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

a. Male participants must agree to not donate sperm from the time the ICF is signed until 15 months after the last IMP administration. Contraceptive requirements are provided in Appendix 4, Section 10.4.2.
b. Women of childbearing potential (WOCBP) (defined in Appendix 4, Section 10.4.1.1) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before IMP can be administered

The contraceptive requirements for WOCBP are described in Appendix 4, Section 10.4.2.

5.2. Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

1. Any coexisting condition which may interfere with the outcome assessments (eg, diabetic neuropathy, CIDP, inflammatory arthritis, or osteoarthritis affecting the hand)
2. Clinical signs or symptoms suggestive for neuropathies other than MMN such as motor neuron disease (eg, bulbar signs or brisk reflexes) or other inflammatory neuropathies (eg, sensory neuropathy)
3. Severe psychiatric disorder (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation that in the opinion of the investigator could create undue risk to the participant or could affect adherence with the trial protocol. See Section 8.2.6.

   Note: At screening, suicidality will be assessed using the Columbia-suicide severity rating scale (C-SSRS) (see Section 8.2.6.1); participants with a high suicide risk will be excluded from the trial (ie, participants will be excluded with a positive answer to questions #4 and/or #5 of the suicidal ideation subscale [over the past 3 months]; and/or any positive answer to the suicidal behavior subscale [over the past year]). Any positive answer to the questions under “Lifetime/time he/she felt most suicidal” should be carefully evaluated for any current risk of suicide by the investigator prior to trial entry.

4.2. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection during the screening and/or IVMP.

   - **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 during screening. Rapid antigen testing will only be mandatory if required locally.

5. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of MMN or put the participant at undue risk (eg, SLE).
6. History of malignancy unless resolved by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of the IMP. Participants with the following carcinomas will be eligible:

   a. Adequately treated basal cell or squamous cell skin cancer
   b. Carcinoma in situ of the cervix
   c. Carcinoma in situ of the breast or

d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)

7.1. Clinical evidence of other significant serious diseases, have had a recent major surgery (including a splenectomy at any time), or who have any other condition in the opinion of the investigator, that could confound the results of the trial or put the participant at undue risk

8. Prior/concomitant therapy

a. Cyclophosphamide and/or rituximab and/or eculizumab and/or mycophenolate mofetil within 3 months prior to screening
b. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of the IMP.

9.1. Positive serum test at screening for an active viral infection with any of the following conditions:

a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf) (Table 14)
b. Hepatitis C virus (HCV) based on HCV antibody assay, confirmed by HCV RNA (Table 15)
c. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count <200 cells/mm^3 (Table 16)

10. Current or history of (ie, within 12 months of screening) alcohol, drug, or medication abuse

11. Known hypersensitivity reaction to 1 of the components of the IMP or any of its excipients

12.1. Female participants with a positive serum or urine pregnancy test, lactating females, and those who intend to become pregnant during the trial or within 15 months after last dose of the IMP

13. ALT or AST ≥2 × upper limit of normal and total bilirubin ≥1.5 × upper limit of normal of the central laboratory reference range, or any other clinically significant laboratory abnormality. These tests will be performed by the central laboratory (refer to Section 10.2)

14. An estimated glomerular filtration rate of ≤60 mL/min/1.73m^2 calculated by the central laboratory using the 4-variable Modification of Diet in the Renal-Disease equation (see Section 10.2)

5.3. Lifestyle Considerations

There are no lifestyle restrictions or limitations required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the DBTP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries

from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened 1 time (ie, repeating all of the screening assessments per the SoA, Table 1 Section 1.3) or retested (ie, repeating 1 or more assessments) 1 time after the sponsor's approval.

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

- Individuals who required treatment for an acute illness (eg, infection) may be rescreened once the illness is resolved or the medical problem stabilized.

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

- Individuals who have clinical laboratory tests value meeting 1 or more exclusion criteria which are not in line with the medical history and clinical evaluation of the individual, may be retested to confirm the value of the tests, if still allowed within the screening period. If not feasible, the individual should be rescreened.

Rescreened participants should be assigned a new participant number for every screening/rescreening event.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol.

6.1. Study Intervention(s) Administered

Table 8: Study Intervention(s) Administered

Intervention label	ARGX-117 IV	Placebo IV
Intervention name	ARGX-117 concentrate for solution for infusion [redacted] mg/ml, administered IV	Placebo
Type	Biologic	Other: placebo
Dose formulation	ARGX-117 drug product of [redacted] mg/mL for dosing of IV infusions	Placebo drug product for dosing of IV infusions
Unit dose strength(s)	[redacted] mg/mL	Placebo
Dosage level(s)[a]	Cohort 1: [redacted] Cohort 2: [redacted]	Placebo

	[redacted]	
Route of administration	IV infusion	IV infusion
Use	Investigational	Investigational placebo
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement

AxMP= Auxiliary medicinal product; EC= ethics committee; EDRT=executive data review team; IDMC=independent data monitoring committee; IMP=investigational medicinal product; IRB=institutional review board; IV=intravenous; NIMP=noninvestigational medicinal product; [redacted]

Table 9: Study Arm(s)

Arm Title	Dose regimen 1	Dose regimen for cohort 2			Placebo
Arm Type	Experimental	Experimental			Placebo
		[redacted]	[redacted]	[redacted]	
Arm Description[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]			
Associated Intervention Labels	ARGX-117 IV [redacted]	ARGX-117 IV [redacted]	ARGX-117 IV [redacted]	ARGX-117 IV [redacted]	Placebo

[redacted]

[redacted]

6.2. Preparation, Handling, Storage, and Accountability

For detailed instructions for preparation, handling, storage, and accountability, please refer to the separate pharmacy manual.

6.2.1. Preparation

ARGX-117 for IV administration will be provided as a sterile, clear concentrate in glass vials. A matching placebo is formulated in the same buffer and presented in identical glass vials. Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared by unblinded site staff before administration.

IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) regulations.

6.2.2. Handling

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants enrolled in the trial may receive IMP and only authorized site staff may supply the IMP. IMP administration must be performed by the site staff.

6.2.3. Storage

The IMP will be supplied to the pharmacy (or substitute) at the designated investigational site by and under the responsibility of the sponsor's designated IMP supply vendor. The investigator will be provided with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.

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

The investigator or their designee is responsible for the correct and safe storage of the IMP assigned to the clinical site, in a locked secure storage facility maintained within the appropriate temperature ranges, with access limited to those individuals authorized to dispense IMP.

6.2.4. Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Detailed instructions on accountability of the IMP will be included in the separate pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

In this randomized, controlled trial, participants will be randomized in a 2:1 ratio [redacted] to the study intervention

arms using an interactive voice/web response system (IVRS/IWRS). [redacted]

- [redacted]
- [redacted]

Study intervention will be administered at the trial visits as summarized in the SoA (Section 1.3).

Before the trial is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

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

The EDRT can access unblinded data for the purpose of strategical decision making and planning. Unblinded information will remain confidential to the EDRT and will not be communicated to the blinded trial team, site staff, or participants to mitigate the risk of releasing treatment assignment to sites and participants (see Section 10.1.5.3).

Blinding will be maintained between placebo, dose regimen 1, and dose regimen 2 or 3; however, clinical trial pharmacy personnel will be considered as unblinded to placebo due to the difference of viscosity between placebo and ARGX-117. This discrepancy is eliminated upon dilution of IMP into IV bags. Blinded personnel such as the trial nurse/coordinator or the investigator will have access to IMP only after this dilution has been performed. In addition, for cohort 2, the dose regimen will remain blinded to the site (except the pharmacist) and to the participant. For the [redacted] placebo will be administered on [redacted] to maintain the blinding compared to the [redacted].

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. The sponsor must be contacted within 24 hours of unblinding a participant. The date and reason for the unblinding must be recorded.

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

Sponsor safety staff may unblind the intervention assignment for any participant with an AE, SAE, or adverse event of special interest (AESI). If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

When participants are dosed at the site, they will receive IMP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

If a participant misses 1 or more IMP administrations, the investigator or designee shall discuss the reason with the participant and stress the importance of compliance with IMP administrations. The investigator or designee should discuss missed IMP administration with the medical monitor and sponsor.

6.5. Continued Access to ARGX-117 After the End of the Study

Argenx will comply with all local laws and regulations for ensuring participants have continued access to ARGX-117 that is identified as essential at the end of the trial.

Participants will receive ARGX-117 after the end of this trial if they are eligible and intend to enroll in the LTE, ARGX-117-2003.

After completing the DBTP, participants who meet the inclusion and exclusion criteria of ARGX-117-2003 may enroll in an LTE study (Table 2 Section 1.3) ARGX-117-2003, and receive ARGX-117.

The consent to roll over into the LTE will be obtained during V14. Participants who will roll over into the LTE will have a combination of the V14 visit and the first visit of the ARGX-117-2003 LTE. All participants who roll over into the LTE will be documented on the ARGX-117-2002 eCRF.

The dose to be used in the LTE will be described in the ARGX-117-2003 protocol.

6.6. Medication Administration Error

A variation of ±10% of the intended ARGX-117 dose will be considered an overdose/underdose or medication error. The sponsor does not recommend specific treatment.

A medication error is any preventable incident that may cause or lead to inappropriate IMP use or harm to the participant while the IMP is in the control of the health care professionals. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

In case of suspected overdose or medication error, the participant will be treated according to standard medical practice based on the investigator's judgment. The suspected overdose or medication error with the quantity of the excess dose will be documented in the eCRF including the additional AEs, if any.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the study intervention can no longer be detected systemically.
- Obtain a blood sample for PK analysis within 1 day from the date of the last dose of IMP if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose and the duration of the overdose.

6.7. Use and Administration of IVIg

Participants will receive IVIg during the IVMP and IVDP (if applicable) as described in the SoA (Table 1 Section 1.3).

Participants who demonstrate a clinically meaningful deterioration during the DBTP (Section 8.1.1.1) will be re-treated with IVIg. However, based on their clinical judgment, the investigator may choose to not re-treat the participant with IVIg.

The time-to-relapse is considered the time until a participant meets the threshold for clinical deterioration. It is recommended that a UNS visit occur within 3 business days to administer IVIg. This visit will be considered the time to retreatment with IVIg. The first retreatment with IVIg will be performed according the UNS IVIg visit shown on Table 2. If the timing for subsequent IVIg retreatment does not coincide with a regularly scheduled visit day of the DBTP, a UNS visit will be done for the participant to receive IVIg.

It is recommended to administer the baseline IVIg dose at the initial IVIg retreatment. It is recommended to consider an IVIg dose optimization strategy for subsequent IVIg administrations guided by clinical outcome measures (eg, based on GS, mMRC sum score).

IVIg retreatment does not preclude participants from receiving IMP at the time points scheduled in the SoA (Table 2 Section 1.3). Refer to Section 8.1 for recommendations if IVIg and ARGX-117 are administered on the same day.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant received within 3 months of the trial, receives at the time of enrollment, or receives during the trial must be recorded on the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

All available vaccination history should be recorded as part of the participant's prior medication for vaccinations received in the past, or as concomitant medication for vaccinations received during the trial, as described in the SoA (Section 1.3).

The use of cyclophosphamide and/or rituximab and/or eculizumab and/or mycophenolate mofetil is not permitted (exclusion criterion 8.a).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

The trial shall be immediately suspended and an urgent referral made to the IDMC for expedited advice if:

- Any participant with a treatment-emergent adverse event (TEAE) of Common Terminology Criteria for Adverse Events (CTCAE) grade 5 that is considered related to IMP
- Any 3 participants with TEAEs of CTCAE grade 4 that are considered related to IMP
- More than 2 participants develop a CTCAE grade ≥ 3 toxicity within the same system organ class (SOC) that are considered related to IMP

The final causality assessment will be made by the sponsor after careful review of all relevant information, including recommendations/suggestions from the PI and IDMC.

Termination of specific sites or of the study as a whole are described in Appendix 1, Section 10.1.9.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will enter the safety follow-up period. See the SoA (Table 3 Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the trial at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for behavioral or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the trial, if possible, an early discontinuation (ED) visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of trial discontinuation and follow up and for any further evaluations that need to be completed. The participant will be permanently discontinued from the study intervention and the trial at that time.

If the participant withdraws consent to disclose future information, the sponsor may retain the participant's samples and continue to use any data collected before the participant's withdrawal of consent.

Samples that were collected before a participant withdraws from the trial will be used for assessments described in Section 1.3 but will not be used for future research.

7.2.1. Temporary Discontinuation of IMP

Temporary interruption of IMP occurs when the participant discontinues receiving IMP before the end of the trial and resumes once the cause for the discontinuation has been resolved.

Reasons for temporary discontinuation may include an AE that meets the following criteria:

- Any SAE considered related to IMP by the sponsor
- Clinically significant active infection considered related to the IMP by the sponsor

7.2.2. Early Discontinuation of IMP

Permanent ED from treatment means that the participant stops receiving the ongoing IMP treatment and does not restart IMP treatment, however, informed consent is not withdrawn. These participants will remain blinded and followed during the safety follow-up period to characterize the safety, PK, and PD of ARGX-117 according to the SoA (Table 2 Section 1.3). A participant may be permanently discontinued from further trial medication following discussion with the sponsor and medical monitor in the event of any of the following:

- Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed).
- Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of NCI-CTCAE grade 4 that is considered related to IMP by the sponsor.
- During the DBTP, participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship.
- Use of non-permitted concomitant medication, as defined in Section 6.8.
- Participants for whom the code has been broken by the investigator will be discontinued from IMP, and all efforts should be made to conduct the ED visit and the safety follow-up period unless consent is withdrawn.
- Psychiatric conditions.

  Note: In the case of severe depression, suicidal ideation, or attempted suicide, trial medication must be at least temporarily interrupted until the participant's psychiatric condition has been fully evaluated. A psychiatrist should be consulted whenever necessary. Treatment may be resumed only after consultation with the sponsor.

Participants permanently discontinuing IMP will be ineligible to roll over to the LTE trial.

7.3. Lost to Follow-up

A participant will be considered lost to follow up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the trial.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she may be considered to have withdrawn from the trial following discussion with the medical monitor.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Safety or laboratory results that could unblind the trial will not be reported to investigative sites or other blinded personnel.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Planned timepoints for all the assessments of efficacy are provided in the SoA (Section 1.3).

It is preferred that efficacy assessment are performed before IMP and IVIg administration and in this preferred order:

- GS
- mMRC-14 sum score
- Participant reported outcome measures including: MMN-RODS, EQ-5D-5L, CAP-PRI, PGIC, FSS, HRPQ, and TSQM
- 9-HPT

It is preferred that IMP is administered before IVIg if IVIg and IMP are administered on the same day.

Training for trial staff on efficacy assessments will be provided at the investigator meeting or at the individual site initiation visits if necessary.

All assessments will be recorded electronically.

8.1.1. Assessments of Efficacy, Functional Ability, Arm and Hand Function, Quality of Life, and Fatigue

8.1.1.1. Time to Retreatment With IVIg

Participants will be re-treated with IVIg during the DBTP if there is a clinically meaningful deterioration in muscle strength and/or motor function. However, based on their clinical judgment, the investigator may choose to not re-treat the participant with IVIg.

A clinically meaningful deterioration is defined as a >30% decline in the GS of either hand observed for at least 2 consecutive days (based on the 3-day averaged calculations) and/or a decline of at least 2 points on the mMRC-10 sum score compared to the day of randomization.

The time that a participant reaches this threshold is considered the time-to-relapse. The date and time that IVIg retreatment is administered will be considered the time to retreatment with IVIg (Section 6.7). Both the time-to-relapse and the time to retreatment with IVIg will be recorded.

All trial participants can request IVIg retreatment with the investigator anytime during the DBTP (Section 6.7). The investigator will contact the medical monitor if the participant does not meet the criteria for a clinically meaningful deterioration but requests retreatment with IVIg.

8.1.1.2. mMRC-14 and mMRC-10 Sum Score

The mMRC sum score evaluates motor strength/weakness from predetermined muscle groups (upper and lower limbs). It is recommended that a participant is scored on the mMRC sum score by the same evaluator during trial visits.

The scoring system of the mMRC sum score and the muscle groups tested for each mMRC sum score is provided in Table 10 and Table 11, respectively.

Table 10: Scoring of the mMRC Sum Score

[redacted]

[redacted]

8.1.1.3. Grip Strength

The Martin vigorimeter will be used for measurement of GS once at the screening visit and daily during the IVDP (if applicable), IVMP, and DBTP.

Each daily GS measurement will consist of 3 repeated contractions with the participant's maximal effort. The duration of each contraction will be 3 seconds. It is recommended for each test to begin with the participant gripping with the right hand followed by the left. The tests will be performed in the following recommended order: 3 repetitions will be executed consecutively by the right hand followed by 3 repetitions of the left hand. There will be a 30-second rest period between each of the 3 repetitions and a 2-minute rest period between each hand.

The participants will perform all GS tests in a seated position: participants will be comfortably seated in a chair without arm rests, with feet fully resting on the floor, hips as far back in the

chair as possible, and the hips and knees positioned at approximately 90°. The shoulder of the tested extremity will be adducted and neutrally rotated, the elbow flexed at 90°, the forearm in neutral position and the wrist between 0° and 30° of dorsiflexion and between 0° and 15° of ulnar deviation. Participants will be instructed to maintain their position during the GS test.

Measurements will be assessed and reported by the trial physician during on-site trial visits. It is recommended that a participant is assessed by the same evaluator during on-site visits. GS will be measured daily throughout the IVDP, IVMP, and DBTP by the participant. The time of day and results will be recorded electronically when performed by the participant. Measurements are recommended to be performed at similar times (preferably in the morning) of the day at each assessment.

The 3 daily measurements of GS from the left hand and the 3 daily measurements of GS from the right hand will be recorded and the daily average for the left hand and right hand will be calculated, respectively. A 3-day moving average will be generated based on the average of the obtained averages for each hand. The daily moving average will consist of day -2, day -1, and day 0.

8.1.1.4. Rasch-built Overall Disability Scale

The MMN-RODS is a disease specific PRO instrument constructed specifically to capture activity limitations in patients with MMN. It consists of 25 items that are scored 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without difficulty) for each item yielding a total score from 0 to 50.[20]

The 25-item MMN-RODS is provided in Appendix 7, Section 10.7.1.

8.1.1.5. 9-Hole Peg Test

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function. Both the dominant and non-dominant hands will be tested twice (2 consecutive trials of the dominant hand, followed immediately by 2 consecutive trials of the non-dominant hand). All participants should receive training in assessing the 9-HPT before the start of the trial, to exclude any training effect.[21] It is recommended that a participant is assessed by the same evaluator during on-site visits.

Directions for the 9-HPT are provided in Appendix 7, Section 10.7.2.

8.1.1.6. EQ-5D-5L

The EQ-5D-5L questionnaire is a standardized test recognized by many health authorities as a generic measure of health status for clinical and economic appraisal. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores for each dimension include 5 levels: no problem, slight problem, moderate problem, severe problem, and extreme problem.

A vertical VAS is included in the EQ-5D-5L. Participants mark their health status from 0 (the worst health you can imagine) to 100 (the best health you can imagine).[22]

A preview of the EQ-5D-5L questionnaire is provided in Section 10.7.3.

8.1.1.7. Chronic Acquired Polyneuropathy Patient-Reported Index

Next to general QOL, disease specific QOL will be assessed through the CAP-PRI. This instrument includes the assessment of 15 items. Items will be scored 0 (not at all), 1 (a little bit) or 2 (a lot) yielding a total score that ranges from 0 to 30.[23] The CAP-PRI scale is provided in Section 10.7.4.

8.1.1.8. Patient Global Impression Change

The PGIC is a patient-reported outcome, which was published in 1976 by the National Institute of Mental Health (US).

The self-report measure PGIC reflects a patient's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement. The PGIC that will be used for this trial is provided in Section 10.7.5.[24]

8.1.1.9. Fatigue Severity Scale

The FSS is a 9-item self-reported questionnaire scale developed in 1989 and designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. 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. The scoring is done by calculating the average response to the questions (adding all answers and dividing by 9). The FSS questionnaire is provided in Section 10.7.6.[25]

8.1.2. Health-Related Productivity Questionnaire

The HRPQ was originally developed in patients with Parkinson's disease to provide data related to missed hours at work or educational activities and reduced effectiveness during any attempted work.[26] These criteria form an important portion of work-related productivity and will be used to assess health-related and work-related productivity in this trial.

8.1.3. 14-Item Questionnaire for Medication

The original version (version 1.4) of the TSQM questionnaire was developed in 2004 to measure patients' satisfaction with their medication using 4 scales (side effects, effectiveness, convenience, and global satisfaction) and will be used in this trial.[27]

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, and neurological systems.

A brief physical examination will include, at a minimum, assessments of the skin, lymph nodes, and musculoskeletal extremities.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically significant abnormalities in physical examination at screening will be reported as medical history on the eCRF. At all other trial visits, new abnormal or worsened pre-existing conditions which are clinically significant as judged by the investigator, will be reported as an AE.

8.2.2. Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed (Section 1.3).

Height, weight, and BMI will be performed during the screening period. Weight will be measured at IMV3 (Section 1.3).

Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

8.2.3. Electrocardiograms

Triplicate 12-lead ECG(s) will be obtained at screening and V1. Single 12 lead ECGs will be obtained at all other scheduled time points as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

Blood samples for laboratory assessments will be collected according to the procedures of the central laboratory.

The samples will be analyzed using routine methods at the local certified laboratory at the site or at a central laboratory.

Further details of collection, handling, storage, and transportation of the samples will be described in the separate laboratory manual.

During the screening period, out of range clinical safety laboratory test values that will determine a participant's eligibility can be repeated following approval from the medical monitor.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all scheduled time points throughout the trial. Clinically relevant findings observed after signing

informed consent and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on an AE page of the eCRF.

Chronic inhibition of C2 could potentially decrease the ability of the immune system to clear immune complexes, which could lead to an increased risk of SLE.

- An ANA test will be performed at the SLE sampling time points indicated in the SoA (Section 1.3), 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 antiU1RNP) will be evaluated from the blood samples collected. Clinical significance will be assessed by the PI in consultation with the relevant clinical specialists (ie, rheumatologist).
  - The presence of ENA autoantibodies will only be reported if ANA ≥1:100

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, Section 10.2 must be conducted in accordance with the instructions provided in the separate laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the AE details and outcomes must be reported to the sponsor.

8.2.5. Pregnancy Testing

Female participants must have pregnancy tests performed and their follicle-stimulating hormone (FSH) level measured at the time points provided in the SoA (Section 1.3).

- A serum pregnancy test must be performed at screening
- A urine pregnancy will be performed at all other timepoints provided in the SoA for WOCBP
- A negative pregnancy test must be documented prior to the first IMP administration

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

ARGX-117 is being developed for MMN which is a neurologic condition. Participants treated with ARGX-117 should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention.

Participants who report signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with ARGX-117 will be alerted about the need to monitor participants for the emergence of unusual changes in behavior, and the emergence of SIB and to report such symptoms immediately to the trial investigator.

Baseline assessment of SIB and intervention-emergent SIB will be monitored as described in sections Section 8.2.6.1 and Section 8.2.6.2.

8.2.6.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

At screening, suicidality will be assessed using the C-SSRS for SIB risk assessment and monitoring. The questionnaire is included in Appendix 9, Section 10.9. Individuals with a high suicide risk will be excluded from the trial. Patients with a high suicide risk are defined as with a positive answer to questions #4 and/or #5 of the suicidal ideation subscale (over the past 3 months); and/or any positive answer to the suicidal behavior subscale (over the past year). Any positive answer to these questions under “Lifetime/Time he/she felt most suicidal” should be carefully evaluated for any current risk of suicide by the investigator prior to trial entry.

Suicidality will be assessed according to Section 8.2.6.2.

8.2.6.2. Suicidality Assessment During the Trial

The suicidality assessment will be conducted by specifically answering the following question, derived from the Patient Health Questionnaire 9 (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?”

The participant will be asked this question at the time points specified in the SoA (Section 1.3) and the response will be documented. Response options as per the PHQ-9 are limited to the following: “not at all,” “several days,” “more than half the days,” or “nearly every day.”

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

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, a surrogate, or the participant’s legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up SAEs, considered related to the study intervention or trial procedures, or that caused the participant to discontinue from randomized treatment or from the trial (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last trial visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3.The investigator will submit any updated information to the reported SAE/AESI to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the study intervention or trial participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs as defined in Section 8.3.6 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives a safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IEC/IRB, if appropriate according to local requirements.

The sponsor (or its designee) will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authorities and IEC/IRB, as per applicable regulatory requirements. The sponsor (or its designee) will also be responsible to forward SUSAR reports to all investigators involved in the trial, who will be required to report these SUSARs to their respective IECs/IRBs, as per their local regulatory requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 15 months after the last administration of IMP.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The participant (and, if consented, the pregnant female partner of a participant), will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant or pregnant female partner and the neonate and the information will be forwarded to the sponsor.

While the investigator is not obligated to actively seek posttrial pregnancy related SAE in former trial participants or pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the trial will discontinue IMP.

8.3.6. Adverse Events of Special Interest

An AESI is an event of scientific and medical concern specific to the sponsor's product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. An AESI can be serious or non-serious and related or unrelated to trial IMP or procedures. Further characterizing information will be collected in the eCRF.

ARGX-117 inhibits C2 and downstream complement activation; long-term complement inhibition can increase the risk of infection with encapsulated bacteria. As such, severe infection events (CTCAE grade ≥ 3) are considered AESIs in this trial to be communicated to the sponsor in a way similar to that of SAEs. Information to be collected will include:

- Causal pathogen

- Location of the infection
- Relationship to the underlying condition, medical history, and concomitant medications
- Reoccurrence of previous infection
- Any confirmatory procedure, culture, or urgent medical intervention.

8.3.7. Adverse Events of Clinical Interest

8.3.7.1. Hypersensitivity and Local Administration Site Reactions

All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. As with any SC or IV injection, injection- or infusion-related reactions can occur during or after administration.

The ARGX-117 IB provides more information on hypersensitivity and local administration site reactions.

8.4. Pharmacokinetics

Blood samples will be collected for measurement of serum concentrations of ARGX-117 as specified in the SoA (Section 1.3).

[redacted] are not mandatory and are considered optional visits. A minimum of 14 participants per cohort are targeted to attend the optional visits.

Blood samples will be collected according to the local standard procedures. Information on equipment and further details on the procedures on sample collection are documented in a separate laboratory manual.

Instructions for the collection and handling of biological samples will be provided by the sponsor.

Samples collected for analyses of ARGX-117 concentration may also be used to evaluate safety or efficacy aspects related to scientific questions arising during or after the trial.

The concentrations of ARGX-117 in serum will be determined using a validated enzyme-linked immunosorbent assay.

The serum PK parameters for ARGX-117 will be derived by non-compartmental analysis of the serum concentration-time profiles using the actual collection times.

The PK parameters, definitions, and the methods of calculation are as follows:

$AUC_{0\text{-}t}$	AUC from time zero to time t of the last measured quantifiable concentration calculated using the linear-up/logarithmic-down trapezoidal method
$AUC_{0\text{-}xh}$	AUC from time zero to x hours after IMP administration, calculated using the linear-up/logarithmic-down trapezoidal method

AUC_{∞}	AUC from time zero to infinity, calculated form $AUC_{0-t} + (C_t/\lambda_z)$, where C_t is the last observed quantifiable concentration and λ_z is the terminal elimination rate constant
C_{max}	maximum observed serum concentration
C_{xh}	concentration at x hours post dose
T_{max}	time to reach C_{max}
$t_{½}$	apparent terminal half-life
V_z(/F)	(apparent) volume of distribution
CL(/F)	(apparent) total clearance

Dose-normalized parameters including C_{max}/dose and AUCs/dose will be assessed.

8.5. Pharmacodynamics

Blood samples will be collected for the determination of free C2 concentrations, total C2 concentrations and functional complement activity (CH50) as indicated in the schedule of activities (Section 1.3). [redacted] are not mandatory and are considered optional. A minimum of 14 participants per cohort are targeted to attend the optional visits.

Blood will be collected according to the specialty lab standard procedures. Information on equipment and further details on the procedures on sample collection are documented in the separate laboratory manual.

These PD markers will be determined using assays which are validated for their intended use.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the trial. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the trial.

- DNA will be isolated from blood samples for single nucleotide polymorphism (SNP) analysis including complement regulatory proteins.
- Samples will be collected according to the schedule described in the SoA (Section 1.3) and as described in a separate laboratory manual (Section 8.7).

See Appendix 5, Section 10.5 for information regarding genetic research. Details for collection, shipment, and destruction of these samples can be found in the separate laboratory manual.

[redacted]

[redacted]

8.9. Immunogenicity Assessments

Immunogenicity blood samples that are collected at the screening visit may only be used for methodology validation and/or for future research purposes. Such use of these samples is only permitted after obtaining consent from the participant; this is described further in the ICF.

Samples may be stored for a maximum of 15 years (or according to local regulations).

8.9.1. Assessments of Anti–ARGX-117 Antibodies

Blood samples will be collected at the time points specified in the SoA (Section 1.3) to evaluate serum levels of ADA against ARGX-117. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened and confirmed for ADA against ARGX-117 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ARGX-117.

Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ARGX-117.

8.9.2. Anti-ARGX-117 Neutralizing Antibodies

Neutralizing antibodies to ARGX-117 can be evaluated in the collected serum samples and banked from all participants according to the SoA (Section 1.3).

Samples will be stored for future use for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ARGX-117.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to the database lock for analysis of the DBTP and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypotheses

Given the exploratory nature of the trial, no formal hypothesis testing will be performed.

9.1.1. Multiplicity Adjustment

No multiplicity adjustment will be applied in this trial considering the exploratory nature of the trial. P-values, if presented, will have to be interpreted descriptively.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Safety analysis set (SAS)	All participants who were randomized and who received at least 1 dose of IMP (ARGX-117 or placebo). Participants will be analyzed according to the treatment they actually received.

The SAS is used to analyze both safety and efficacy.

9.3. Statistical Analyses

9.3.1. General Considerations

[redacted] Blinding of the individual participants enrolled into the safety follow-up will be ensured (actual treatment of individual participants will not be shared with the site or participant) as long as any participant is undergoing the safety follow-up. The final analysis will be performed when all participants complete the safety follow-up and will solely describe the safety data collected during the safety follow-up period. The clinical study report will cover all data collected [redacted]. These will be reported separately. A final database lock will occur when all participants have completed the safety follow-up period, or have rolled over to the LTE study, if applicable.

For the analysis, each ARGX-117 dose regimen will be analyzed separately while data from the placebo arms will be pooled to form a unique placebo arm. In general, results will be tabulated by treatment group and stratification factor and presented using both descriptive and inferential statistics. P-values, if presented, will be interpreted descriptively given the exploratory nature of the current trial.

Categorical data will be described using absolute and relative frequencies. Continuous variables will be summarized using the following standard descriptive summary statistics: number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. Shift tables will be provided where appropriate.

More details on the planned analyses and endpoints and the handling of missing data will be described in the SAP, which will be finalized before database lock of the first interim analysis.

9.3.2. Primary Endpoint

The safety analyses will be performed using the SAS. Safety variables include AEs, clinical laboratory variables, vital signs, concomitant medications, and suicidal behavior.

For calculation of changes from baseline, the last value collected before to the first dose of IMP will be used as baseline.

9.3.2.1. Adverse Events

AEs will be coded using the newest version of MedDRA in effect at the start of the trial.

An AE (classified by preferred term) that occurs during the DBTP will be considered a TEAE if it has a start date on or after the first dose of IMP or if it has a start date before the date of the first dose of IMP but increases in severity on or after the date of the first dose of IMP. If more than 1 AE with the same preferred term is reported before the date of the first dose of IMP, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the DBTP under the preferred term.

A summary of the number of participants with TEAEs (including AESIs) will be presented, including the number and percentage of participants with any TEAEs, serious TEAEs, TEAEs related to IMP and TEAEs leading to discontinuation of IMP.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by SOC and preferred term, and by SOC, preferred term, and maximum severity. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same preferred term for the same participant, then the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to IMP.

9.3.2.2. Vital Signs and Electrocardiograms

Descriptive statistics for vital signs, ECG results, changes from baseline for each assessment time point, and shift tables from baseline to each visit for quantitative variables will be presented by treatment groups. Abnormalities for each variable will be listed separately.

9.3.2.3. Clinical Laboratory

Descriptive statistics for clinical laboratory values and changes from baseline at each assessment time point and shift tables from baseline to each visit for quantitative variables will be presented by treatment group. Frequency tables will be created for qualitative tests. Abnormal laboratory tests results will be listed separately.

9.3.3. Secondary Endpoints

The efficacy analyses will be performed using the SAS.

Secondary endpoints are defined as follows:

- Time to the first retreatment with IVIg since the final IVIg treatment of the IVMP
- Time-to-relapse, defined as the time from randomization until at least 1 criterion for clinical deterioration is met (GS or mMRC-10)

mMRC

- AUC of the change from baseline in the mMRC-10 sum score
- Value and change from baseline in the average score of the 2 most important muscle groups as assessed by the mMRC-14 sum score
- Value and change from baseline in the mMRC-14 sum score
- 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

Grip Strength

- AUC of the change from baseline in GS
- Proportion of participants with a GS decrease of 8 kPa or more over 3 consecutive days
- Values, change, and % change from baseline in GS

[redacted]

The same analysis for time-to-relapse will also be performed. Time-to-relapse is defined as the time until a participant meets the threshold for clinical deterioration.

To correct for differences in trial durations, the endpoints based on AUC will be standardized to an average AUC per week (7 days).

[redacted]

In addition, the following secondary efficacy endpoints will also be described per visit in the SAS as appropriate

- Values and change from baseline in the MMN-RODS
- Values and change from baseline in the average time for the upper extremity (arm and hand) function (9-HPT, or timed pegboard test)
- The 5 dimensions assessed by the EQ-5D-5L are: mobility, self-care, usual activities, pain/discomfort, and anxiety depression. Each dimension will be described as number and proportion of participants by level of severity, and value and change from baseline in EQ-5D-5L VAS
- Values and change from baseline in the CAP-PRI
- Values of the PGIC scale
- Values and change from baseline in the FSS
- HRPQ
  - The following items for both work-related (for full-time or part-time employed participants) and household chore activities (for all participants) will be described using the value at each visit[26]:
    - Hours lost because of absenteeism
    - Hours lost because of presenteeism
    - Total hours lost (absenteeism + presenteeism)
    - Percentage of scheduled hours lost because of absenteeism
    - Percentage of scheduled hours lost because of presenteeism
    - Percentage of scheduled hours lost in total (absenteeism + presenteeism)
- Effectiveness, side effects, convenience, and overall satisfaction scores as assessed by the TSQM

The following PK, PD and immunogenicity parameters will be summarized:

- Serum concentrations and PK parameters for ARGX-117
- Values and change from baseline in free C2, total C2, CH50
- Incidence and prevalence of ADA against ARGX-117

Population PK and PD analyses may be performed and reported in a separate report.

More details on secondary endpoints analysis, derived from available information, will be defined in the SAP.

[redacted]

9.3.5. Independent Data Monitoring Committee

Details on IDMC are provided in Section 10.1.5.2.

9.3.6. Other Analyses

All secondary endpoints will also be presented per subgroup based on the stratification variable.

9.4. Sample Size Determination

Given the exploratory nature of this trial, no formal sample size calculation will be 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 deemed sufficient to respond to the primary objective. A sample size of 16 participants receiving ARGX-117 (for 1 cohort) has a 56% probability of detecting an AE with an incidence of 5%. This probability increases to 97% if the incidence rate of AE is 20% (Table 12).

Table 12: Probability of Detecting an Adverse Event According to Sample Size and Incidence Rate

Adverse Event Incidence Rate	Sample Size	
	16	32
0.05	0.56	0.81
0.10	0.82	0.97
0.15	0.93	0.99
0.20	0.97	1

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the trial, including the risks and benefits, to the participant or their legally authorized representative (according to local regulations) and answer all questions regarding the trial.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial, and the date that the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that address the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees' Structure

10.1.5.1. Independent MMN Confirmation Committee

The MCC will review the investigator's diagnosis of MMN during the screening period. The MCC will ensure that the trial population fulfills the criteria for probable or definite MMN according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 guidelines (Appendix 8, Section 10.8).

The MCC may request additional assessments to support the confirmation of diagnosis if the information in the participant's medical history is insufficient to confirm a probable or definite MMN diagnosis per the EFN/PNS 2010 guidelines.

Individuals for whom the diagnosis cannot be confirmed will be ineligible for this trial.

The MCC will assess the IVIg dependency criterion. If IVIg dependency is uncertain, the participant will enter an additional period to assess dependency following a delayed administration of IVIg and continue into a subsequent IVMP once the IVIg dependency criterion has been fulfilled.

The MCC will be composed of neurologists with expertise in the diagnosis and treatment of MMN. A trial participant profile will be developed and presented for MCC review, as described in the MCC charter.

All trial sites will be trained and instructed on the MCC review process.

IVIg treatment dependency will be based on the following:

- Recently initiated IVIg treatment (less than 3 months):
  - Clinical improvement following IVIg initiation documented in the participant's medical record
- Maintenance therapy with IVIg (longer than 3 months):
  - Clinical deterioration following IVIg withdrawal, IVIg dose reduction, or IVIg delayed administration within 12 months prior to screening (documented in the participant's medical record)
  - Clinical deterioration following IVIg delayed administration during the IVDP

10.1.5.2. Independent Data Monitoring Committee

The IDMC will monitor accumulating safety data. Committee composition will depend on the scientific skills and knowledge required for trial monitoring and will include at least 3 independent members, including a statistician.

The IDMC will review and evaluate safety data and make recommendations on continued dosing within a cohort, the opening of cohort 2, and modification or discontinuation of the trial. At minimum, the IDMC will conduct a review of the accumulated data at the following scheduled time points:

- [redacted]

- [redacted]
- [redacted]

Additional participants screened and eligible for cohort 2 before the decision to open cohort 2 is made will be assigned to cohort 1.

- Participant safety will be continuously monitored by the IDMC, which includes safety signal detection at any time during the trial.
- All safety data collected will be summarized and reviewed by the IDMC
- In particular, data will be reviewed by the sponsor for identification of the following events that would potentially contribute to a recommendation to pause or stop the trial.
  - Any deaths, regardless of causality
  - Other

The IDMC will recommend further actions to be taken if a pausing or stopping rule is met. Refer to the IDMC/EDRT charter for further details.

10.1.5.3. Executive Data Review Team

The EDRT can access unblinded data for the purpose of strategical decision making and planning, including but not limited to the decision to open cohort 2 following recommendations from the IDMC. Unblinded information will remain confidential to the EDRT and will not be communicated to the blinded trial team, site staff, or participants to mitigate the risk of releasing treatment assignment to sites and participants.

[redacted]

Refer to the IDMC/EDRT charter for more information regarding the EDRT.

10.1.6. Dissemination of Clinical Study Data

Trial information and tabular trial results will be posted on US National Institutes of Health's website www.clinicaltrials.gov, on the European Clinical Trials database website www.clinicaltrialsregister.eu, and other publicly accessible sites.

10.1.7. Data Quality Assurance

- All participant data relating to the trial will be recorded on an eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data and

electronic clinical assessment data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.

- Guidance on completion of eCRFs will be provided in investigator site file.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of trial critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan
- The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Participant reported outcomes (Section 8.1) and grip strength (GS) will be entered into an electronic clinical outcome assessment (eCOA) platform or web portal and will be considered source data.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.
- The definition of what constitutes source data and their origin can be found in the investigator source data agreement
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being

protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The first act of recruitment is the first site activation and will be the trial start date.

Study/Site Termination

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of planned participants is reached earlier than expected

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow up.

10.1.10. Publication Policy

- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual

site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 13 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the participant's medical record.
- Protocol-specific requirements for inclusion or exclusion of participants are described in Section 5.
- Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 13: Protocol-Required Safety Laboratory Tests

<table>
<tr><th>Laboratory Test</th><th colspan="4">Parameter</th></tr>
<tr><td rowspan="4">Hematology</td><td>RBC</td><td rowspan="4">RBC indices:
• MCV
• MCH
• %reticulocytes</td><td colspan="2" rowspan="4">WBC count with differential:
• neutrophils
• eosinophils
• lymphocytes
• basophils
• monocytes</td></tr>
<tr><td>platelet count</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="4">Clinical chemistry</td><td>BUN</td><td>potassium</td><td>AST/SGOT</td><td>total protein</td></tr>
<tr><td>Creatinine</td><td>sodium</td><td>ALT/SGPT</td><td>total and direct bilirubin</td></tr>
<tr><td>glucose (fasting or nonfasting)</td><td>calcium</td><td>ALP</td><td rowspan="2">creatine kinase (when elevated, CK-MB to be assessed)</td></tr>
<tr><td>total IgG</td><td>eGFR</td><td>C-reactive protein</td></tr>
<tr><td>Coagulation</td><td colspan="4">international normalized ratio only</td></tr>
<tr><td>Routine analysis</td><td colspan="4">1. Specific gravity
2. pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
3. Microscopic examination (if blood or protein is abnormal)</td></tr>
</table>

Laboratory Test	Parameter
Pregnancy testing	Highly sensitive serum and urine human chorionic gonadotropin pregnancy test (as needed for WOCBP, defined in Appendix 4)[a]
SLE Panel	To be performed at the time points specified in the SoA (Section 1.3). 1. ANA (titer and staining pattern) 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
Other screening tests	see Section 10.2.1

ALP=alkaline phosphatase; ALT/SGPT=alanine aminotransferase/ serum glutamic pyruvic transaminase; ANA=antinuclear antibody; AST/SGOT=aspartate aminotransferase/serum glutamic-oxaloacetic transaminase; BUN=blood urea nitrogen; CK-MB=creatine kinase myocardial band; DNA=deoxyribonucleic acid; eGFR=estimated glomerular filtration rate; ENA=extractable nuclear antigen antibodies; IEC=independent ethics committee; IgG=immunoglobulin G; IRB=institutional review board; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cells; SLE= systemic lupus erythematosus; WBC=white blood cells

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.2.1. Other Screening Tests

10.2.1.1. Hepatitis B Virus

Participants with active, acute, or chronic hepatitis B virus (HBV) at screening cannot be enrolled in the trial.

The following combinations of serologic markers will be used to identify an active HBV infection (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf):

Table 14: Interpretation of Hepatitis B Serological Test Results

Test Result			Interpretation
HBsAg	Anti-HBc	Anti-HBs	
Positive	Positive	Negative	The participant cannot be enrolled in the trial because the test results indicate an active HBV infection.
Negative	Positive	Negative	The participant cannot be enrolled in the trial because the test results indicate a low level chronic HBV infection with impaired liver function.[a]

anti-HBc=total hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus

[a] This decision will be made by a medical doctor with sufficient expertise in hepatology or infectious disease. Additional tests (eg, HBV viral load) may be required to determine the status of the patient.

10.2.1.2. Hepatitis C Virus

Participants with active, acute, or chronic hepatitis C virus (HCV) at screening cannot be enrolled in the trial. Tests for HCV will be used to identify an active HCV infection as indicated in Table 15.

Table 15: Interpretation of Hepatitis C Test

HCV Ab test result	Interpretation	Further actions
HCV Ab nonreactive	No HCV Ab detected	Sample can be reported as nonreactive for HCV Ab. No further action required. If recent exposure in person tested is suspected, test for HCV RNA.[a]
HCV Ab reactive	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV Ab. Test for HCV RNA to identify current infection.
HCV Ab reactive, HCV RNA detected	Current HCV infection	Provide person tested with appropriate counseling and link person tested to care and treatment.[b]
HCV Ab reactive, HCV RNA not detected	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV Ab is desired, and if sample is repeatedly reactive in the initial test, test with another HCV Ab assay. In certain situations,[c] follow up with HCV RNA testing and appropriate counseling.

Source: Centers for Disease Control and Prevention[32]
HCV=hepatitis C virus; HCV Ab=hepatitis C virus antibody

[a] If HCV RNA testing is not feasible and person tested is not immunocompromised, perform follow-up testing for HCV Ab to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

[b] Before initiating antiviral therapy, it is recommended to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

[c] Examples of these situations may include if the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

10.2.1.3. Human Immunodeficiency Virus

Participants who are HIV positive and do not have an AIDS-defining condition or a CD4 count >200 cells/mm^3 at screening can be enrolled in the trial (see Table 16). Participants who are HIV positive and have an AIDS-defining condition or a CD4 count ≤200 cells/mm^3 at screening cannot be enrolled in the trial. The following are considered AIDS-defining conditions:

- Cytomegalovirus retinitis with loss of vision
- *Pneumocystis jirovecii* pneumonia
- Chronic intestinal cryptosporidiosis
- HIV-related encephalopathy
- *Mycobacterium tuberculosis* (pulmonary or extrapulmonary)
- Invasive cervical cancer

Table 16: Interpretation of HIV Test Results in Combination With the Participant's Clinical Condition and CD4 Count

HIV Test Result	Clinical Condition or CD4 Count	Interpretation
Positive	AIDS-defining condition is present or CD4 count <200 cells/mm^3	The participant cannot be enrolled in the trial because test results and clinical condition or CD4 count confirm the diagnosis of AIDS.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events to Be Collected as AEs
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the trial • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

Events <u>NOT</u> to Be Collected as AEs
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen

10.3.2. Definition of SAE

An SAE Is Defined as Any Untoward Medical Occurrence That, at Any Dose, Meets One or More of the Criteria Listed:

1. Results in death

2. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline will not be collected as an AE.

4. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include reports of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the previous section. These events should usually be considered serious.
  - — Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.
  - — Suspected transmission of any infectious agent via the medicinal product will also be treated as an SAE.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator will assess intensity for each AE and SAE reported during the trial.

All AEs observed will be graded using the current version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

The grade refers to the severity of the AE. If a particular AE's severity is not specifically graded by the guidance document, the investigator is to use the general NCI CTCAE definitions of grade 1 through grade 5 following his or her best medical judgment, using the following general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4: Life-threatening consequences or urgent intervention indicated
- Grade 5: Death related to AE

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE as **related** or **not related**. The investigator will use

clinical judgment to determine whether there is reasonable possibility that the IMP or IVIg retreatment caused the AE.

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, and the temporal relationship of the event to study intervention administration, will be considered and investigated.
- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP administration or IVIg retreatment is compelling and/or follows a known or suspected response pattern concerning that medication.
- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP or IVIg retreatment and the AE.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs/AESIs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide a copy of any postmortem findings to the sponsor, including histopathology, if available.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE/AESI data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs and AESIs

SAE/AESI Reporting via a Paper Report Form
• All SAEs and AESIs will be recorded (within 24hours) on the paper SAE/AESI report form and the AE form on the electronic case report form (eCRF). • The investigator or delegated site staff should check that all entered data is consistent. • An alert email for the SAE/AESI report on the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the electronic data capture system. • The paper SAE/AESI report form should be faxed or emailed to the sponsor's designated CRO (see the Safety Mailbox/Fax details on the title page of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential

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

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

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for Women of Childbearing Potential

WOCBP must use a highly effective contraceptive method which should be maintained at minimum until 15 months after last dose of IMP.

The same type of hormonal contraception must have been received for at least 1 month before starting this trial.

Highly effective methods of contraception are:

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    a. Oral
    b. Intravaginal
    c. Transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation:
    a. Oral
    b. Injectable
    c. Implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence: a highly effective method only if defined as refraining from heterosexual intercourse from the time the ICF is signed until 15 months after the last dose of IMP. The reliability of sexual abstinence needs to be evaluated relative to the duration of the study and the preferred and usual lifestyle of the participant. Sexual abstinence can be used only if it is the preferred and usual lifestyle of the participant.

10.4.2.2. Male Contraception

Male participants must use an acceptable contraceptive method which should be maintained at minimum until 15 months after last dose of IMP.

Acceptable methods of contraception are:

1. A condom
2. Sexual abstinence: a highly effective method only if defined as refraining from heterosexual intercourse from the time the ICF is signed until 15 months after the last dose of IMP. The reliability of sexual abstinence needs to be evaluated relative to the duration of the study and the preferred and usual lifestyle of the participant. Sexual abstinence can be used only if it is the preferred and usual lifestyle of the participant
3. Bilateral vasectomy (only if confirmed to be a medically successful surgery)

Males cannot donate sperm while receiving IMP.

10.4.2.3. Unacceptable Forms of Contraception

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational amenorrhea method are not acceptable methods of contraception.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to ARGX-117 or MMN and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to study intervention, interventions of this drug class and MMN. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be collected to assess for the presence of SNPs in patients with MMN. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to ARGX-117 or interventions of this drug class to understand the trial disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate trial summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study intervention continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: List of Abbreviations

Abbreviation	Explanation
9-HPT	9-Hole Peg Test
ADA	antidrug antibody
ADL	activities of daily living
AEs	adverse events
AESIs	adverse events of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibody
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAP-PRI	chronic acquired polyneuropathy patient-reported index
CH50	functional complement activity
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
C-SSRS	Columbia-suicide severity rating scale
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	double-blinded treatment period
DNA	deoxyribonucleic acid
eCOA	electronic clinical outcome assessment
ED	early discontinuation
EDRT	(unblinded) executive data review team
EFNS	European Federation of Neurological Societies
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	Euro-Quality of Life 5 Dimensions 5 Levels
ENA	extractable nuclear antigen antibodies
FIH	first-in-human

Abbreviation	Explanation
FSH	follicle-stimulating hormone
FSS	9-item Fatigue Severity Scale
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
[redacted]	[redacted]
GMP	Good Manufacturing Practice
GS	grip strength
HBV	hepatitis B virus
HCV	hepatitis C virus
[redacted]	[redacted]
HRPQ	Health-Related Productivity Questionnaire
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IECs	independent ethics committees
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational medicinal product
IRBs	institutional review boards
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenously
IVDP	IVIg dependency period
IVIg	intravenous immunoglobulin
IVMP	IVIg monitoring period
IVRS	interactive voice response system
IWRS	interactive web response system
kPa	Kilopascal
[redacted]	[redacted]
LTE	long-term extension

Abbreviation	Explanation
MAC	membrane attack complex
MCC	MMN Confirmation Committee
MMN	multifocal motor neuropathy
MMN-RODS	Rasch-built overall disability scale for MMN
mMRC	modified Medical Research Council
NCI	National Cancer Institute
[redacted]	[redacted]
NOAEL	no observed adverse effect level
PD	pharmacodynamics
PGIC	Patient Global Impression Change
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetics
PNS	Peripheral Nerve Society
RBC	red blood cell
RDT	repeat-dose toxicity
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneously
SIB	suicidal ideation and behavior
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SoA	Schedule of Activities
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
T_{max}	time to reach C_{max}
TSQM	Treatment Satisfaction 14-Item Questionnaire for Medication
WBC	white blood cell
WOCBP	women of childbearing potential

10.7. Appendix 7: Assessments of Efficacy

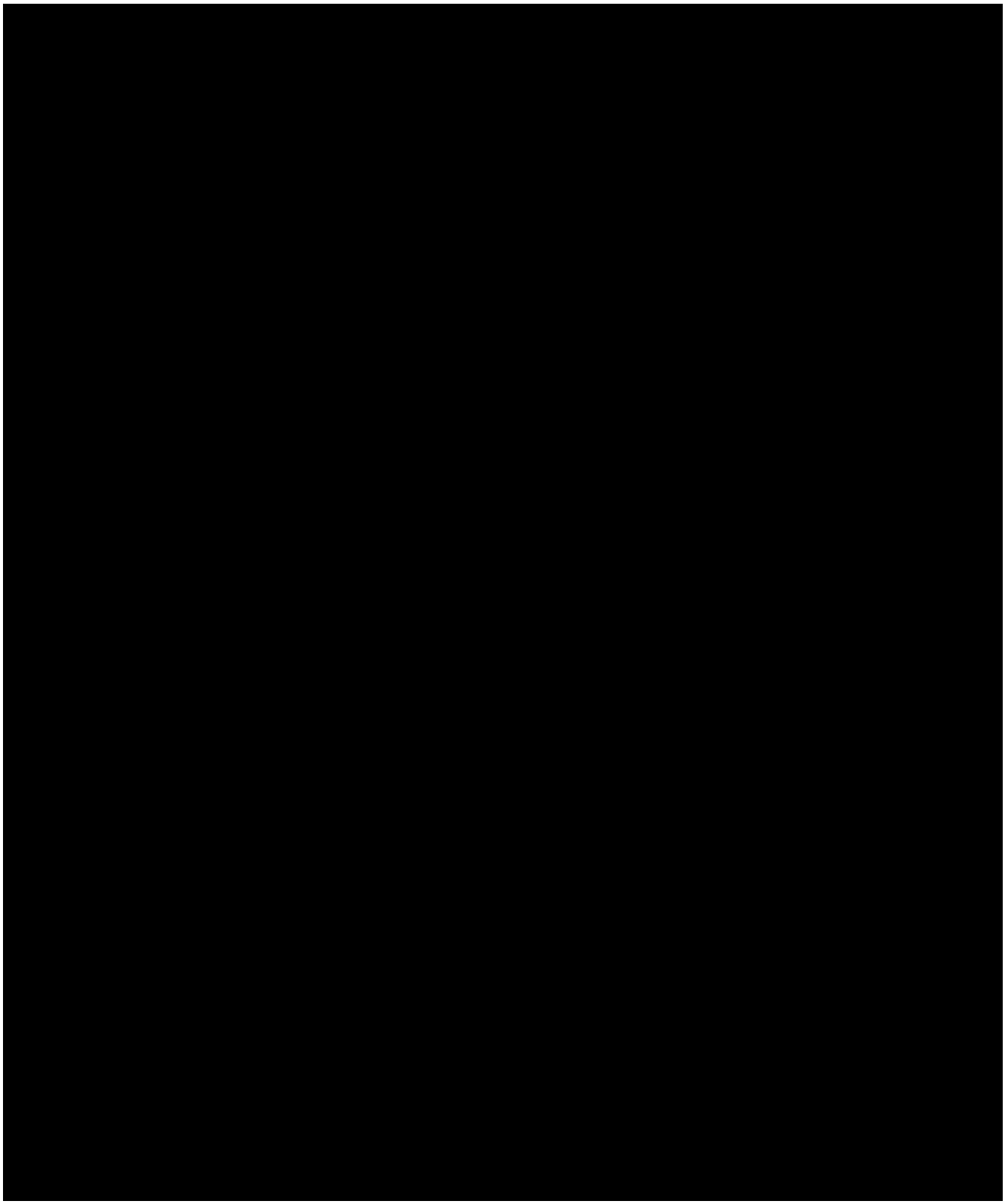
[redacted]

10.7.2. 9-HPT

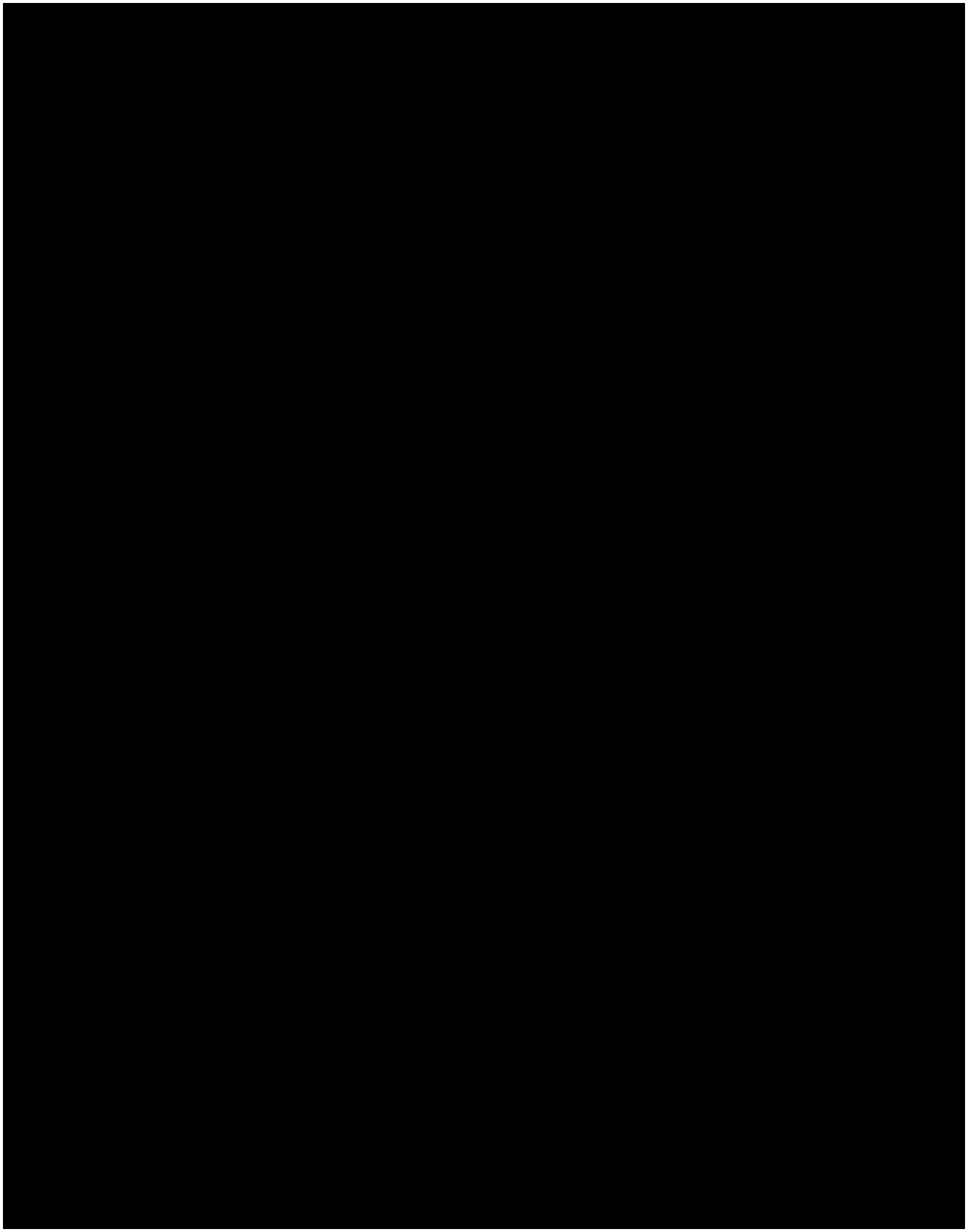
[redacted]

[redacted]

10.7.3. EQ-5D-5L



10.7.4. CAP-PRI



10.7.5. PGIC

10.7.6. FSS Questionnaire

Source: The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus[31]

10.8. Appendix 8: Probable or Definite Diagnostic Criteria for MMN

[redacted]

Table 19: Electrophysiological Criteria for Conduction Block

[redacted]

[redacted]

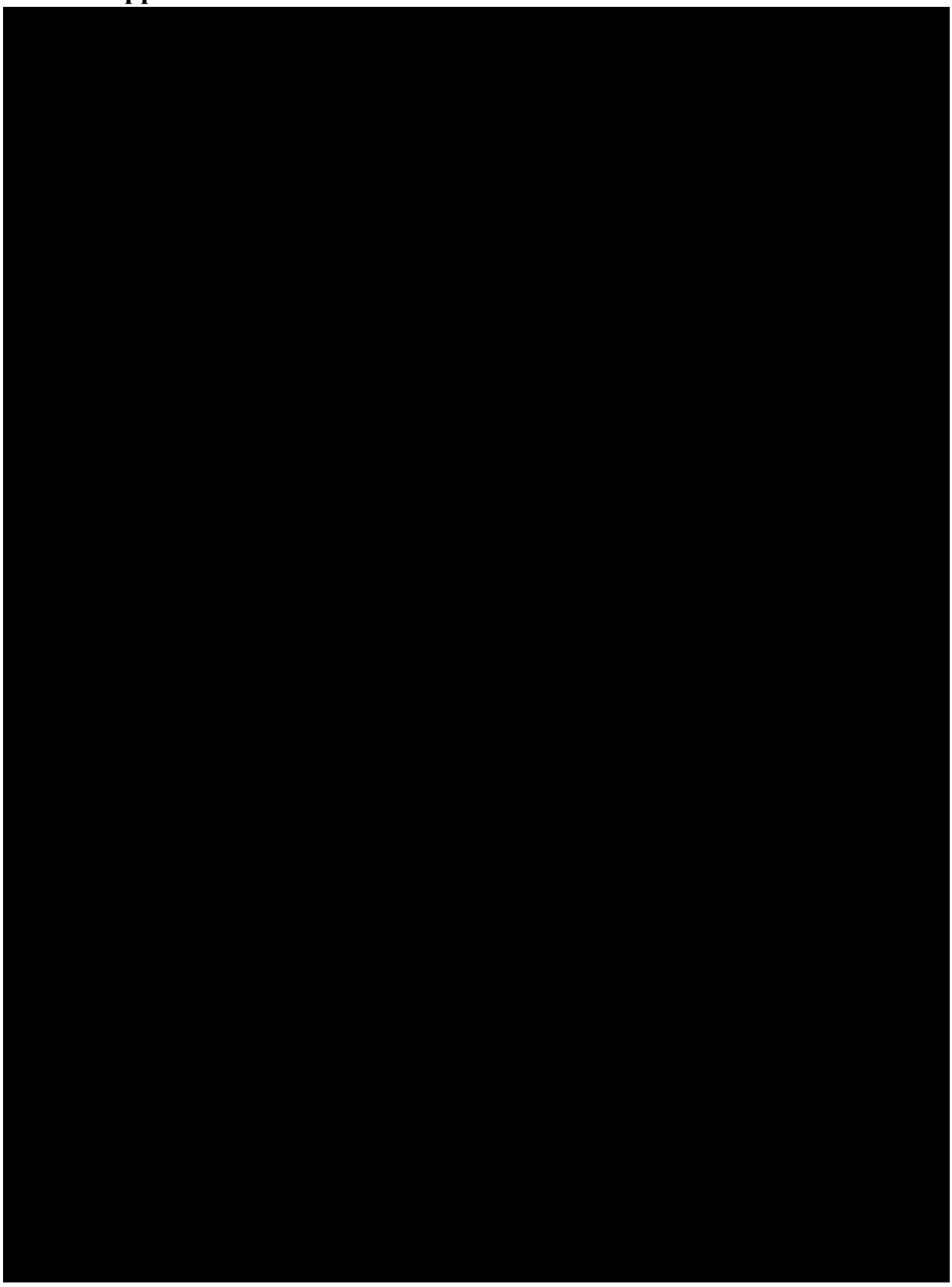
Table 20: Supportive Criteria

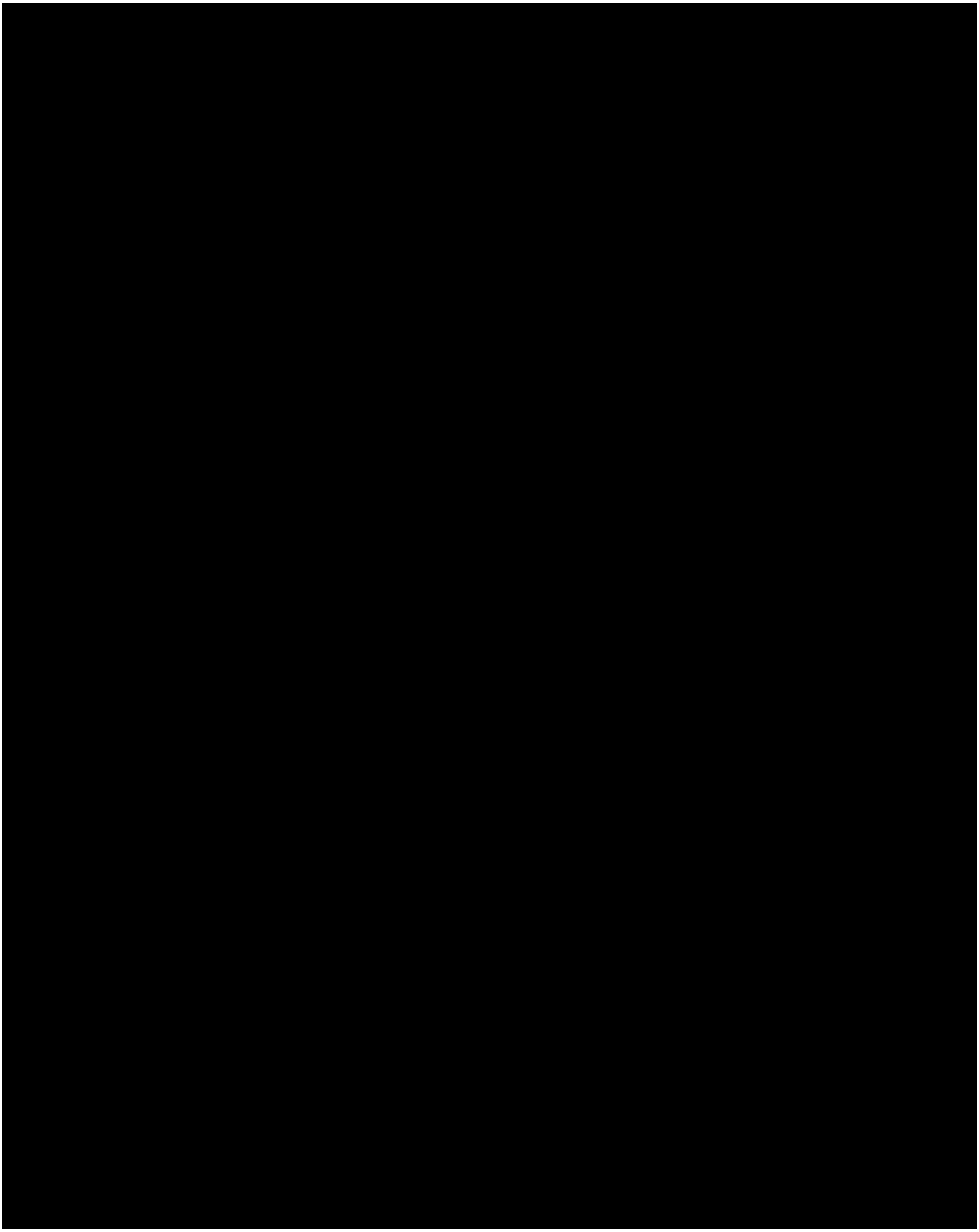
[redacted]

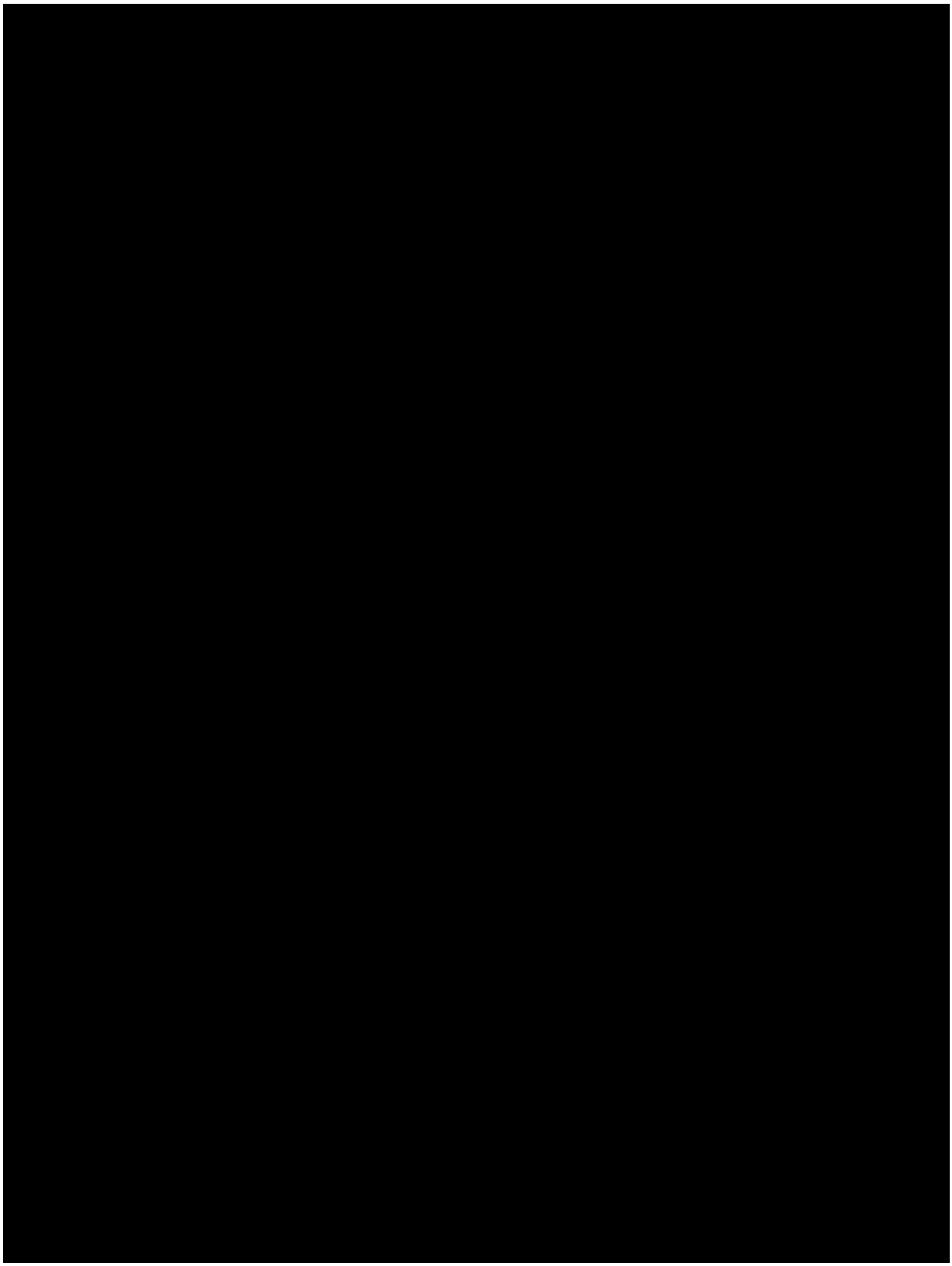
Table 21: Diagnostic Categories for MMN

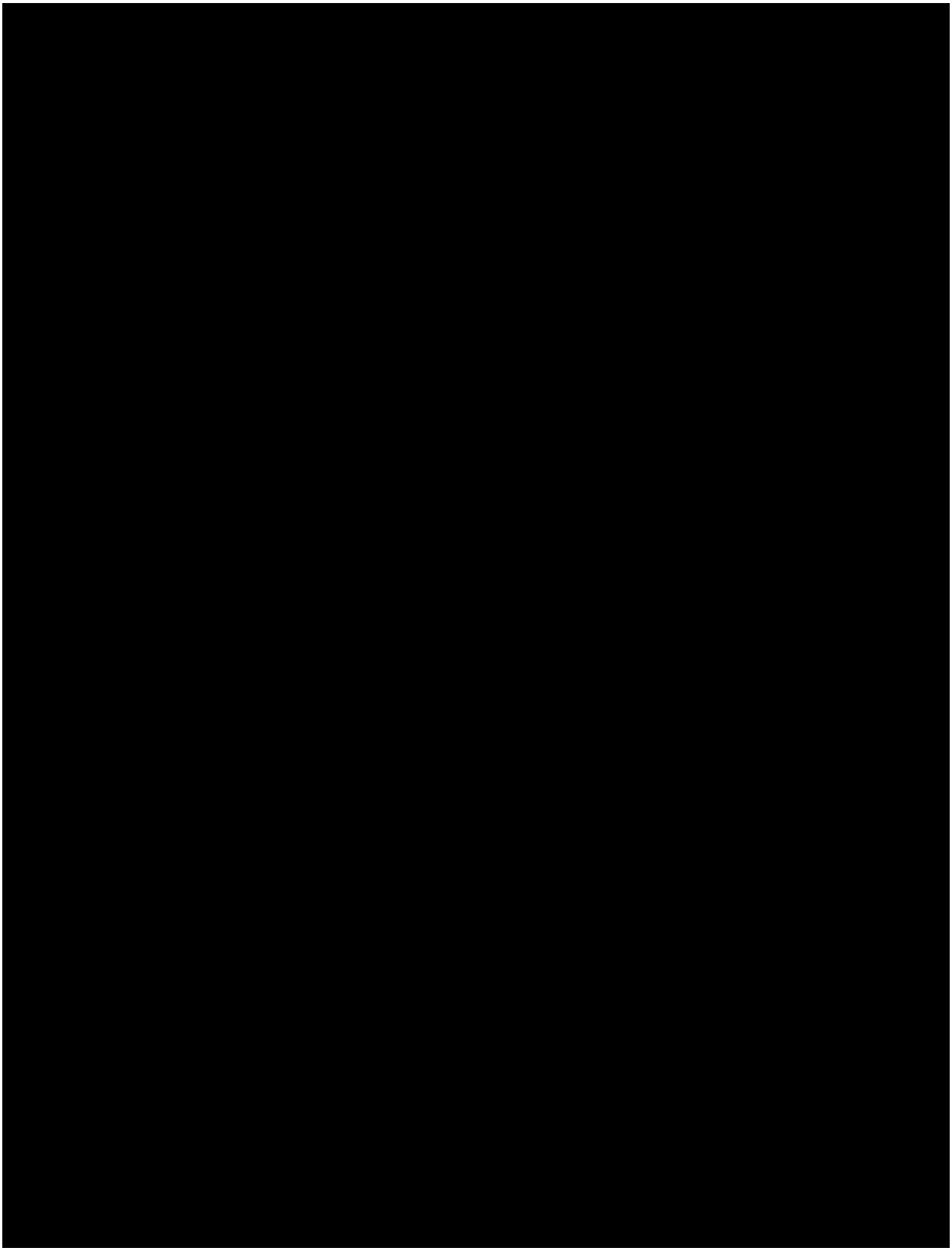
[redacted]

10.9. Appendix 9: C-SSRS









10.10. Appendix 10: Country-specific Requirements

Germany: Additional COVID-19 precautions are to be taken. These precautions are incorporated in Sections 1.3, 2.3.3, 5.1, and 5.2.

10.11. Protocol Amendment History

The Protocol Amendment Summary of Changes for the current amendment is located directly before the Investigator's Acknowledgment.

Amendment 2: (12 Dec 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Changes were implemented to reflect the data from the first-in-human (FIH) study of ARGX-117. Significant changes between protocol version 2.0 and version 3.0 are summarized in the following table. A strikethrough indicates deleted text, and bold font indicates added text. Administrative and editorial changes (eg, to improve readability) are not presented. Refer to Section 10.6 for any undefined abbreviations.

Section	Description of change	Brief rationale
1.1, Synopsis 3, Objectives and Endpoints 4.1.2, IVIg Dependency Period 4.1.4, Double-Blinded Treatment Period 4.2, Scientific Rationale for Study Design 8.1.1.1, Time to Retreatment With IVIg	[redacted]	[redacted]
1.1, Synopsis 3, Objectives and Endpoints 4.1.4, Double-Blinded Treatment Period 6.7, Use and Administration of IVIg 8.1.1.1, Time to Retreatment With IVIg 9.3.3, Secondary Endpoints	Participants will be re-treated with IVIg during the DBTP if there is a clinically meaningful deterioration… **Based on their clinical judgment, the investigator may choose to not re-treat the participant with IVIg.** • **Time-to-relapse** • **Time-to-relapse, defined as the time from randomization until at least 1 criterion for clinical deterioration is met (GS or mMRC-10)** ~~A sensitivity~~ **The same analysis** for time-to-relapse will also be performed.	The investigator will determine if the deterioration in objective MMN measurements necessitates retreatment with IVIg. The endpoint time-to-relapse has been added to allow for the assessment of the time to objective clinical deterioration if there is a delay between when the participant meets the defined thresholds for clinically meaningful deterioration and actual IVIg retreatment.
1.1, Synopsis Table 3 4.1, Overall Design 4.2, Scientific Rationale for Study Design 5.1, Inclusion Criteria	The half-life of ARGX-117 ranged from approximately 70 to 88 days WOCBP must use the highly effective contraceptives for ~~12~~ **15** months after the final administration of IMP The safety follow-up period will be ~~12~~ **15** months long	Available data from the FIH study reflect an ARGX-117 half-life of 70 to 88 days. The safety follow-up period and the contraceptive

Section	Description of change	Brief rationale
5.2, Exclusion Criteria 8.3.5, Pregnancy 10.4, Appendix 4, Contraceptive and Barrier Guidance	Inclusion criterion 7.1a Male participants must agree to not donate sperm from the time the ICF is signed until ~~12~~ **15** months after the last IMP administration. Exclusion Criterion 12.1 Female participants with a positive serum or urine pregnancy test, lactating females, and those who intend to become pregnant during the trial or within ~~12~~ **15** months	requirements were updated to 15 months to reflect the half-life.
10.4.2.2, Male Contraception	**Bilateral vasectomy (only if confirmed to be a medically successful surgery)**	A bilateral vasectomy is considered an effective form of contraception.
5.1, Inclusion Criteria	Inclusion criterion 7.1a **Contraceptive requirements are provided in Appendix 4, Section 10.4.2.**	A reference to the male contraceptive requirements has been included for clarity.
7, Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	The trial shall be immediately suspended and an urgent referral made to the IDMC for expedited advice if any of the following occur: • Any ~~isolated~~ **participant with a treatment-emergent adverse event (TEAE) of** Common Terminology Criteria for Adverse Events (CTCAE) ~~severity~~ grade 5 ~~treatment-emergent adverse event (TEAE)~~ that is considered related to IMP • Any 3 **participants with** TEAEs of CTCAE ~~severity~~ grade 4 that are considered related to IMP **The final causality assessment will be made by the sponsor after careful review of all relevant information, including recommendations/suggestions from the PI and IDMC.**	The stopping rules were clarified to apply to participants. It has been clarified that the AE's relation to IMP is determined by the sponsor.
2.2.2, Clinical	Refer to the **current** ARGX-117 IB for ~~additional~~ information **on the PK, PD, and safety of ARGX-117.**	The current ARGX-117 IB has the most up-to-date information on ARGX-117
5.1, Inclusion Criteria	Inclusion criterion 4.1 Receiving a stable IVIg regimen **for at least 3 months** before screening **or recently initiated IVIg treatment (refer to inclusion criterion 5.1a),** Inclusion criterion 5.1 IVIg treatment dependency confirmation by the MCC at screening	To standardize the definition and duration of "stable" IVIg regimen.

Section	Description of change	Brief rationale
	or ~~at IMV1~~ **after IVDP when applicable**,	
Table 12	~~If ALP is elevated, consider fractioning~~	Fractioning will not be performed
Table 2	The notation "(X)" has been introduced to indicate that an assessment will be performed at the discretion of the investigator.	Parentheses have been added to emphasize that these assessments are to be performed at the discretion of the investigator.
Tables 1, 2, and 3 5.1, Inclusion Criteria 5.2, Exclusion Criteria 2.3.3, COVID-19 10.10, Appendix 10: Country-specific Requirements	Germany only: SARS-CoV-2 testing is only mandatory if required locally	To reduce COVID-19 testing burden if it is not considered required locally.
1.1, Synopsis 4.1, Overall Design 10.1.5.2, Independent Data Monitoring Committee 1.2, Schema	The IDMC will conduct a review of the accumulated data when 9 participants in cohort 1 have completed **or discontinued early from** the 16-week DBTP	The second meeting review of the IDMC will also account for early discontinuations within the DBTP.
10.1.5.1, Independent MMN Confirmation Committee	**The MCC may request additional assessments to support the confirmation of diagnosis if the information in the participant's medical history is insufficient to confirm a probable or definite MMN diagnosis per the EFN/PNS 2010 guidelines.**	The MCC may request additional testing if a diagnosis cannot be confirmed.
5.2, Exclusion Criteria 10.2.1.2, Hepatitis C Virus Table 14	HCV testing algorithm and results interpretation were added per the CDC Exclusion criterion 9.1b Hepatitis C virus (HCV) based on HCV antibody assay**, confirmed by HCV RNA**	HCV RNA can be used to confirm and exclude active HCV per current guidelines.
Tables 1 and 2 4.1.3, IVIg Monitoring Period	**Note: All assessments will be performed before IVIg administration unless otherwise specified**. **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**.	Clarified the timing of the assessments. Defined what would happen if a clinically meaningful deterioration occurred between IDV1 and IDV2.

Section	Description of change	Brief rationale
	IMV1 will coincide with ~~when a participant would receive their~~ **the participant's regularly** scheduled ~~dose of~~ IVIg **administration and will be the participant's next regularly scheduled IVIg visit after IDV2 if they entered the IVDP**.	Defined what would occur if a participant received IVIg over multiple days.
	IVIg may be administered over several days according to the local standard of care. All IVIg administrations must occur within the specified visit windows.	Text regarding IVIg administration over several days has been added to account for the variation in the local IVIg standard of care.
	The length of the IVMP may be greater if a participant receives IVIg over the course of several days. **Note: V1 will be 7 days after the final day of IVIg administration for IMV3 (Table 1).**	The amount of time for IVIg infusions can differ between participants.
	A research sample must be collected both before and ~~2h after the start of IVIg administration~~ **immediately after the end of the** IVIg administration. **Research sample collection is optional if the participant receives IVIg at home.**	Research samples will be optional for participants who receive IVIg at home to reduce the patient burden.
	Grip strength will be measured on-site at all trial visits and monitored daily **starting from the IVDP or IVMP (Section 8.1.1.3**).	Clarified the timing of grip strength measurements.
7.2, Participant Discontinuation/Withdrawal From the Study	Samples collected before a participant discontinues from the trial will not be destroyed and may still be used. These samples will not be used for future research.	The sponsor would like to be able to analyze collected, untested samples that have not yet been analyzed at the time of consent withdrawal because analyses are performed in batches, and the corresponding batch test may be planned after the participant's decision to withdraw.
Tables 1, 2, 3, and 12 8.2.4, Clinical Safety Laboratory Tests	The presence of ENA autoantibodies will always be evaluated but will only be reported if ANA ≥1:80	ENA autoantibodies will only be reported if ANA is above the indicated threshold. This reduces the turnaround time for the SLE panel results without affecting the total

Section	Description of change	Brief rationale
		collected blood volume or patient safety.
Table 2 8.1, Efficacy Assessments	All assessments will be performed before IMP or **IVIg** administration unless otherwise specified.	Clarified that the assessments should also occur before IVIg administration.
Tables 4, 5, and 6	PK/PD samples will not be collected 6 hours postdose on [redacted]	[redacted]
3, Objectives and Endpoints 9.3.3, Secondary Endpoints	The secondary endpoints of this study have changed • ~~Difference between the time to the first retreatment with IVIg (cycle) and the second time to retreatment with IVIg~~ • ~~Change~~ **Value and change** from baseline in **the average score of** the 2 most important muscle groups as assessed by the mMRC-14 sum score • Values and change from baseline in **the average time for the** upper extremity (arm and hand) function (9 Hole Peg Test [9-HPT], or timed pegboard test) • ~~Values and change from baseline in quality of life using~~ **Proportion of participants by level of severity on each dimension of the EQ-5D-5L scale** • **Value and change from baseline in EQ-5D-5L visual analog scale (VAS)** • Values ~~and change from baseline in~~ **of** the Patient Global Impression Change (PGIC) scale A more in-depth description of the HRPQ has been added • ~~Values and change from baseline in~~ **Effectiveness, side effects,**	Difference between the time to the first retreatment with IVIg (cycle) and the second time to retreatment with IVIg are unlikely to be meaningful and thus will not be analyzed. The mMRC, 9-HPT, EQ-5D-5L, PGIC, HRPQ, TSQM, and ADA endpoints have been clarified.

Section	Description of change	Brief rationale
	convenience, and overall satisfaction scores as assessed by the Treatment Satisfaction 14-Item Questionnaire for Medication (TSQM) • ~~Serum titer levels of binding antibodies (BAbs)~~ **Incidence and prevalence of ADA** against ARGX-117	
8.1.1.6, EQ-5D-5L 10.7.3, EQ-5D-5L	The description of the EQ-5D-5L questionnaire has been updated The EQ-5D-5L questionnaire has been added to the appendix	The updated description and questionnaire used in the study has been included.
6.7, Use and Administration of IVIg	Added reference to Section 8.1 for recommendations on the order of IVIg and ARGX-117 administrations if performed on the same day	Clarified the order of ARGX-117 and IVIg administration.
7.2.2, Early Discontinuation of IMP	…all efforts should be made to conduct the ED visit and the safety follow-up period **unless consent is withdrawn**	Clarified that this would not apply if consent is withdrawn.
8.1.1.3, Grip Strength	The Martin vigorimeter will be used for ~~daily~~ measurement of GS **once at the screening visit and daily** during the ~~screening period,~~ **IVDP** (if applicable), IVMP, and DBTP. ~~During these periods, GS will be measured in a standardized manner on a daily basis.~~	Clarified the timing of the GS assessments.
8.9.1, Assessments of Anti–ARGX-117 Antibodies	Blood samples will be collected at the time points specified in the SoA (Section 1.3) to evaluate serum levels of ADA against ARGX-117.	The description was clarified to match the updated ADA endpoint.
8.4, Pharmacokinetics	~~The actual date and time (24-hour clock time) of each sample will be recorded.~~	Detailed instructions on the procedures for sample collection are documented in a separate laboratory manual.
9.2, Analysis Sets 9.3.2, Primary Endpoint 9.3.3, Secondary Endpoints	~~Full~~ **Safety** analysis set There will be no “Per protocol analysis set”	The full analysis set has been replaced by safety analysis set because participants will be analyzed according to the treatment received and not planned. Considering the exploratory nature of the trial, the per protocol analysis set has been deleted.
10.3.3, Recording and Follow-up of AE and/or SAE	Changed to the “current version” of the CTCAE	Clarified the version of the CTCAE in the event of a CTCAE version update.

Section	Description of change	Brief rationale
9.3.1, General Considerations	**Interim analyses may be performed for regulatory interactions.**	To allow for the possibility to have interim analyses for regulatory interactions.
Sponsor Signatory	The chief medical officer has changed from [redacted] to [redacted]	The chief medical officer has changed.

Amendment 1: (16 Feb 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Changes were implemented to address requests and comments from the Competent Authorities of countries where the protocol was submitted. Significant changes between protocol version 1.0 and version 2.0 are summarized in the following table. A strikethrough indicates text that was removed, and bold text indicates text that was added. Administrative and editorial changes (eg, to improve readability, comply with company style guide) are not presented:

Section # and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria, exclusion criterion #12 Section 8.3.5, Pregnancy Section 10.4, Appendix 4: Contraceptive and Barrier Guidance	Revised contraceptive guidelines Use of a highly effective form of contraception has been increased from 9 to 12 months. Female participants with a positive serum or urine pregnancy test, lactating females, and those who intend to become pregnant during the trial or within ~~9~~**12** months after last dose of the IMP. The definition of sexual abstinence has been added: **Sexual abstinence is considered a highly effective method only if the participant refrains from heterosexual intercourse from the time the ICF is signed until 12 months after the last IMP administration.** Unacceptable forms of contraception have been added: **Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and the lactational**	[redacted] The definition of sexual abstinence and unacceptable forms of contraception have been defined per the CTFG guidelines

Section # and Name	Description of Change	Brief Rationale
	amenorrhea method are not acceptable methods of contraception.	
Section 1.1, Synopsis Section 6.1, Study Intervention(s) Administered	Ensured the dose regimen descriptions in Table 7 (Section 6.1) and synopsis matched those in Section 4.3.	The description of the dose regimens was aligned to address comments by a Health Authority
Section 1.3, Schedule of Activities Section 8.2.5, Pregnancy Testing	Clarified text to state that the urine pregnancy test will be performed at all other timepoints provided in the SoA for women of childbearing potential	Only women of childbearing potential will have periodic pregnancy tests
Section 1.3, Table 1 Section 4.1.1, Screening Period	Footnote added to IDV1 and IMV1: **IDV1 will coincide with when a participant would receive their scheduled dose of IVIg.** **IMV1 will coincide with when a participant would receive their scheduled dose of IVIg, and the visit window for IMV1 is not applicable, if the participant does not enter the IVIg dependency period** Text added to screening period: **An additional extension of the screening period to align a participant's subsequent IDV1 or IMV1 with their IVIg dosing schedule will not lead to screen failure.**	Clarified that a delay in the first visit (IDV1 or IMV1) to align with a participants IVIg dosing schedule does not generate a screen failure
Section 1.3, Table 2	**All assessments will be performed prior to IMP dosing unless otherwise specified.**	Clarified the timing of assessments
Section 1.3, Table 1	PD and biomarkers will be sampled before IVIg is administered	Clarified the timing of assessments
Section 1.3, Table 1 Section 8.9, Immunogenicity Assessments	Sampling for immunogenicity has been added to screening	Sampling for immunogenicity will be used for validation purposes and for future research
Section 1.3, Table 6	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Synopsis Section 1.2, Schema Section 1.3, Table 3 Section 4, Study Design	The safety follow-up period has been extended from 9 to 12 months and the timing of the visits has been adapted. [redacted]	Participants will be followed for 12 months instead of 9 months after the final IMP administration to allow for a washout period of approximately 5 times the half-life of ARGX-117 to evaluate the safety, PK, and PD of ARGX-117 after discontinuation of treatment Additional SLE sampling has been added to mitigate the potential risks of SLE in a population with an inhibited complement system [redacted]
Section 6.8, Concomitant Therapy	Removed "~~Any vaccination information that the participant, his/her caregiver, or his/her legally authorized representative can remember should be recorded on the eCRF (with the brand name of the vaccine and date of vaccination, if possible)~~."	Clarified that only available vaccination history will be recorded
Section 7.2, Early Discontinuation	**The detection of a new malignancy during the DBTP** will result in the participant discontinuing IMP.	Participants will be discontinued from treatment at the detection of a new malignancy as complement inhibition may play a role in the pathophysiology of carcinomas
Section 7.2, Early Discontinuation	Participants whose code has been broken will be discontinued from IMP	Participants will be discontinued from treatment but remain within the trial
Section 8.6, Genetics	The description of additional testing following DNA extraction failure has been removed ~~In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent~~	Participants will never be asked for a second test
Section 3, Objectives and Endpoints	"Percentage of time" changed to "Proportion of participants"	The endpoint has been corrected

Section # and Name	Description of Change	Brief Rationale
Section 8.2.4, Clinical Safety Laboratory Tests Table 12	Clarified the description of the SLE test to: • An ANA test will be performed at the SLE sampling time points indicated in the SoA, the titer and staining pattern will be reported • If ANA titer >1:80, the potential presence of ENA autoantibodies	The text was updated for clarity because it was unclear when additional tests should be performed
Section 5.2, Exclusion Criteria	Participants will be excluded from the trial if they present with the following: **ALT or AST ≥2 × upper limit of normal and total bilirubin ≥1.5 × upper limit of normal of the central laboratory reference range, or any other clinically significant laboratory abnormality. These tests will be performed by the central laboratory.** **An estimated glomerular filtration rate of ≤60 mL/min/1.73m^2 calculated by the central laboratory using the 4-variable Modification of Diet in the Renal-Disease equation.**	Specific liver and renal exclusion cut-offs have been added to maintain consistency across all participants
Section 5.2, Exclusion Criteria	Individuals who have had a splenectomy will be excluded from the study	Splenectomized individuals have increased risk for infection with encapsulated bacteria
Section 6.3, Measures to Minimize Bias	"Make every effort" has been removed from the sentence: If the investigator decides that unblinding is warranted, the investigator should ~~make every effort~~ contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant	This has been removed to align with Health Authority comments
Section 6.5.1, ARGX-117 Dose Regimen Upon Rollover Into the LTE	The description of the doses in the LTE has been removed and will instead be described in the LTE protocol.	The dosing in the LTE study will be provided in a separate application for review and approval

Section # and Name	Description of Change	Brief Rationale
Section 7, Discontinuation of Study Intervention and Participant Withdrawal	The stopping rules have been modified: ~~• Any 1 CTCAE severity grade 4 TEAE and any 1 CTCAE severity grade 5 TEAE that are considered related to IMP~~ ~~• Two CTCAE severity grade 4 events of the same TEAE that are considered related to IMP~~ • **Any isolated Common Terminology Criteria for Adverse Events (CTCAE) severity grade 5 treatment-emergent adverse event (TEAE) that is considered related to IMP** • Any 3 TEAEs of CTCAE severity grade 4 that are considered related to IMP • **More than 2 participants develop a CTCAE grade ≥ 3 toxicity within the same system organ class (SOC) that are considered related to IMP**	The safety and monitoring criteria have been updated to align with Health Authority comments
Section 10.1.5.2, Independent Data Monitoring Committee	**The IDMC will recommend further actions to be taken if a stopping or pausing rule is met**	The decision to continue the trial after a stopping or pausing rule is met should be advised by the IDMC
Synopsis Section 10.1.5, Committees' Structure	All text related to an IDMC charter or EDRT charter has been merged to an IDMC/EDRT charter	The respective IDMC and EDRT charters were merged because it was more beneficial from an operational standpoint
Section 4.3, Justification for Dose	Information about the toxicity and NOAEL levels from nonclinical studies has been added	Additional justification for the ARGX-117 dose was provided to align with Health Authority comments
Table 12	Added C-reactive protein to the collected lab parameters	A C-reactive protein test will be performed to expand the safety lab data set and for future scientific value
Section 1.3, Table 1-3 Section 2.3.3, COVID-19 Section 5.1, Inclusion Criteria Section 5.2, Exclusion Criteria Section 10.10 Country-specific requirements	Germany only, additional COVID precautions are to be taken.	Additional COVID precautions are to be taken in Germany at the request of the

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