TITLE PAGE

Protocol Title:	A Phase 2 Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Protocol Number:	ARGX-113-1802
Amendment Number:	4 (protocol version 5.0)
Acronym:	ADHERE
Compound:	Efgartigimod (ARGX-113)
Investigational Medicinal Product:	Efgartigimod PH20 SC (efgartigimod co-formulated with recombinant human hyaluronidase PH20 [rHuPH20] for subcutaneous [SC] administration) / Placebo (placebo with rHuPH20 for SC administration)
Trial Phase:	2
Sponsor:	argenx BVBA Industriepark Zwijnaarde 7 9052 Zwijnaarde (Ghent) Belgium Phone: +32 (0)9 310 34 00
Contract Research Organization:	Pharmaceutical Product Development (PPD) Global Ltd Granta Park, Great Abington Cambridge, CB21 6GQ, United Kingdom Phone: +44 1223 374100
Serious Adverse Event Reporting:	Parexel International 8 Federal Street, Billerica, MA 01821, United States of America
For drug safety reporting, contact the following email address:	
Safety Mailbox/Fax:	Email: safety@argenx.com Fax: +1 (833) 874-7325
Regulatory Agency Identifiers:	EudraCT number: 2019-003076-39
Protocol Approval Date:	12 Oct 2022

NOTIFICATION: POSSIBLE ADAPTATIONS OF TRIAL PROTOCOL DURING THE COVID-19 PANDEMIC

The aim of the ARGX-113-1802 trial is to investigate a new subcutaneous (SC) treatment option for patients with chronic inflammatory demyelinating polyneuropathy (CIDP). This SC treatment consists of efgartigimod with recombinant human hyaluronidase PH20 (rHuPH20) (called efgartigimod PH20 SC) and could offer clinically significant benefits to CIDP patients.

argenx has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. Following careful evaluation, the risk/benefit profile of efgartigimod use in ongoing clinical trials has not changed in the context of this pandemic. This decision was made based on efgartigimod's mechanism of action, the safety data generated to date, and provisions made in all clinical trials with efgartigimod for safety reporting and withholding treatment upon evidence of infection. This assessment will be reviewed regularly to consider new information about the pandemic and the ongoing, continuous assessment of adverse events reported during argenx clinical trials.

During the COVID-19 pandemic, it may not be possible to perform all assessments as planned for this trial (see Schedule of Activities [SoA] in Section 1.3).

In order to provide patients with CIDP the opportunity to continue the trial during the COVID-19 pandemic, an Appendix with possible adaptations to the ARGX-113-1802 trial has been developed so that sites can follow this Appendix in case a patient cannot have a trial visit at the hospital site and a visit at home or an alternative convenient location will be performed. This Appendix describes a minimum number of assessments required to guarantee the safety and well-being of patients during the trial and to secure the collection of the critical parameters for analysis. This Appendix is included in Section 11.12 (Appendix 12) of this protocol.

SIGNATURE OF SPONSOR

Protocol Title: A Phase 2 Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Protocol Number: ARGX-113-1802

Acronym: ADHERE

Sponsor Representative:

See appended signature page

[redacted], MD, PhD — Date

Chief Medical Officer, argenx BVBA

SIGNATURE OF INVESTIGATOR

Protocol Title: A Phase 2 Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Protocol Number: ARGX-113-1802

Acronym: ADHERE

This protocol is a confidential document of argenx BVBA. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx BVBA.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the trial will be conducted.

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

Signature of Investigator: _____ Date: _____
Printed Name: _____
Investigator Title: _____
Name/Address of Site: _____
_____
_____

DOCUMENT HISTORY

Previous version number	Effective date
1.0	30 Oct 2019
2.0 (global protocol amendment 1)	10 Jan 2020
3.0 (global protocol amendment 2)	04 May 2020
4.0 (global protocol amendment 3)	30 Nov 2020
Current version number	
5.0 (global protocol amendment 4)	12 Oct 2022

SUMMARY OF CHANGES

General Amendment 4, Global Protocol Version 5.0 (Current Version):
The major changes from global protocol version 4.0 compared to protocol version 5.0 are summarized in the following table. Added text is shown in **bold** font and deleted text is shown in ~~strikethrough~~ font. Minor editorial changes (eg, to improve readability or correct spelling mistakes) are not included.

Previous protocol amendment summaries of changes are provided in Appendix 13 in Section 11.13. Country-specific protocol amendment summaries of changes are provided in Appendix 14 in Section 11.14.

Summary of Changes Between Protocol Version 4.0 and Protocol Version 5.0

Section(s)	Change	Rationale
• First page	• The following changes were made to the drug safety reporting section on the first page: Safety mailbox/fax updated as follows: Email: ~~248700ADR@parexel.com~~ safety@argenx.com Fax: ~~+1 833 644 0806~~ **+1 (833) 874-7325**	The email address and fax number for drug safety reporting have been updated.
• SIGNATURE OF SPONSOR	• [redacted], MD, PhD is now the sponsor signatory for this protocol.	Effective 01 Apr 2022, Dr [redacted] became the sponsor's Chief Medical Officer.
• Section 1.1, Section 1.3, Section 9.10, Section 9.12, Section 10.4.1.5, Section 10.4.2.5, Section 11.2, Section 11.12.1	• The following change was made throughout the protocol: Measurements of IgG subtypes (IgG1, IgG2, IgG3, and IgG4) were removed. Pharmacodynamic analysis includes the measurement of total IgG only (and not of IgG subtypes).	The correlation between total IgG and IgG subtypes has been studied extensively in other efgartigimod trials, is consistent between patient populations, and is well understood. There is no specific scientific need to study the IgG subtypes in CIDP.
• Section 1.1, Section 4.1.2, Section 4.2.2, Section 10.4.1.7 (new section), Section 10.4.2.7 (new section), Section 10.4.3.1, Section 10.5.6 (new section)	• The following change was made in these sections: The EQ-5D-5L (as part of PRO) has been escalated from an exploratory endpoint to a secondary endpoint.	This change was made because EQ-5D-5L is an important parameter for evaluating quality of life. Escalating it to a secondary endpoint allows its use in some countries for health economics evaluations.
• Section 1.1, Section 5.1.4, Section 5.6, Section 7.7	• The following change was made in these sections: Patients who are in run-in at the time of the 88th event, ie, when the trial will stop, will also be given the option to roll over to the OLE trial after performing an early discontinuation visit.	This change was made to allow patients in run-in, ie, who have not received efgartigimod PH20 SC yet, to roll over to the OLE trial ARGX-113-1902 when the current trial ends.
• Footnotes in Schedules of Activities in	• The following was added to the footnote for "Blood sampling for PK and PD analysis" in the Schedules of Activities for Screening, Run-in, and Stage A, and for	Local IgG testing would allow for potential unblinding of the administered IMP during Stage B

Section(s)	Change	Rationale
Section 1.3.1, Section 1.3.2, Section 11.12.1, Section 9.10	Stage B and Follow-up (normal and During COVID-19 Pandemic): **… IgG testing must not be performed locally.** • Section 9.10. Pharmacodynamics was revised to add the following: **Note that local IgG testing must not be performed.**	(efgartigimod PH20 SC or placebo).
• Section 1.1, Section 6.1, Section 6.2, Section 11.3	• The following changes have been made in these sections: – The inclusion criterion regarding the period of contraception use for WOCBP was updated: An acceptable method of contraception should now be used from signing the ICF until the date of the last IMP dose (instead of from baseline to 90 days after the last IMP dose). – The previous inclusion criterion for male patients to not donate sperm during the trial period and 90 days thereafter was deleted. – The exclusion criterion that women cannot become pregnant until at least 90 days after the last IMP dose was updated to not becoming pregnant during the trial.	These changes are based on nonclinical teratogenicity and reprotoxicity data.
• Section 1.1, Section 1.2, Section 10.3	• The following change was made in Section 1.1. Synopsis and Section 1.2. Schema (footnote): Approximately 360 patients aged 18 years and older are planned to be enrolled in Stage A ~~with a maximum of 180 randomized patients in Stage B~~. • The following change was made in Section 1.1. Synopsis and Section 10.3. Sample Size Determination: ~~A maximum of 180 patients will be randomized in order to observe the 88 events in Stage B.~~ **To obtain a sufficient number of patients randomized into Stage B, up to approximately 360 patients would be required to be enrolled into Stage A. Patients will continue to be randomized into Stage B until 88 events are observed as per the sample size calculation, the trial will end when the 88th event is observed.**	In this event-driven trial, a total of 88 events are required to detect a hazard ratio of 0.5 with 90% power at a 1-sided alpha level of 0.025 using a log-rank test. The protocol has been updated to avoid ambiguity in the number of patients that need to be randomized to observe 88 events. This depends on several factors and cannot be exactly estimated (this protocol provides several scenarios under various assumptions around the median time to event). This change also clarifies that up to approximately 360 patients are expected to be enrolled in Stage A to ensure that the number of patients randomized in Stage B will be sufficient to observe the required 88 events.
• Section 3.3.2	• Section 3.3.2. Risks was updated to align with the current argenx protocol template.	These changes to the Risks section reflect additional safety data that have become available since the start of the trial.
• Section 5.1.1, Section 11.1.6, Section 11.5	• Section 5.1.1. Screening: **Note that additional assessments may be asked for to support the confirmation of CIDP diagnosis (see Section 11.1.6).** • Section 11.1.6. CIDP Confirmation Committee (CCC):	These changes clarify that additional tests may be performed to confirm the CIDP diagnosis.

Section(s)	Change	Rationale
	In case the information provided to the CCC is not sufficient to confirm a definite or probable CIDP diagnosis per the EFNS/PNS 2010 criteria,2 additional assessments may be asked for (as listed in Section 11.5 Appendix 5) to support the confirmation of diagnosis. • Section 11.5. Appendix 5: CIDP Diagnostic Tests was added. • Addition of Table 2 from the EFNS/PNS 2010 Guideline,[2] which lists possible investigations to confirm CIDP diagnosis.	
• Section 5.1.1.1, Section 7.4, Section 9.1.1, Section 11.1.3, Section 11.4.1	• Deletion of legally authorized/acceptable representative (according to local regulations).	This trial is for adult patients capable of giving consent, and therefore, a legally authorized/acceptable representative is not needed.
• Section 5.3	• Section 5.3. Justification for Dose has been updated.	This section has been updated with the currently available data.
• Section 7.2	• The following change was made in Section 7.2. Preparation, Handling, Storage, Administration, and Accountability: Instructions about confirming appropriate temperature conditions were deleted, and a cross-reference to the Pharmacy Manual was added for further details.	New temperature stability data allow the IMP to be stored under less strict conditions.
• Section 7.3	• The following was added in Section 7.3. IMP Compliance: In case of lack of compliance, **the number of missed doses will be captured, but the patient can remain in the trial (unless the patient withdraws his/her consent)**.	This change clarifies that the patient can remain in the trial if there is a lack of IMP compliance. This is to avoid unnecessary dropouts.
• Section 1.1, Section 6.2, Section 7.4.2	• Exclusion criterion #9 was updated to include: • **Patients who (intend to) use prohibited medications and therapies (see Section 7.4.2) during the trial.** • The following change was made to Section 7.4.2. Prohibited Medications: • **Use of complementary therapies, including traditional Chinese medicines and herbal remedies, containing any of the following: naturally derived glucocorticoids; medication with clinical evidence-based immunosuppressive, immunomodulatory, peripheral or central nervous system effects; or procedures (eg, acupuncture) for any neurological condition within 4 weeks or 5 half-lives (whichever is longer) prior to IMP dosing and agreed not to use during the trial.**	Prohibited medications and therapies were updated to align this section among all geographic areas.
• Section 8.2	• The following change was made in Section 8.2. Permanent Early Discontinuation of IMP:	This change clarifies when a patient needs to discontinue IMP permanently.

Section(s)	Change	Rationale
	• ~~Development of an SAE that is likely to result in a life-threatening situation or pose a serious safety risk.~~ • **Patient develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion, or an AE of CTCAE grade 4 that is considered related to IMP by the sponsor.**	
• Section 9.5.3, Section 11.2	• The following changes were made in Section 9.5.3. Clinical Safety Laboratory Assessments: • The samples will be analyzed at a centralized certified laboratory. **In the exceptional circumstances that samples cannot be sent to a central laboratory, a local laboratory can be used.** • Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial**, with the exception of total protein and albumin results after the Stage B baseline visit, which will be kept blinded for the site**. **A system will be implemented to notify the investigator in case of out-of-range values to allow for appropriate safety follow-up.** • The following footnote was added to "Total protein" and "Albumin" in Section 11.2. Appendix 2: Clinical Laboratory Tests: **In the exceptional circumstances that using a central laboratory is not possible: Do not measure total protein and albumin after the Stage B baseline visit.**	These changes clarify the following: • A local laboratory can be used in the exceptional circumstance that a central laboratory cannot be used. • As an additional blinding precaution, total protein and albumin results from a central laboratory will not be sent to the site after the Stage B baseline visit, and total protein and albumin must not be measured after the Stage B baseline visit if a local laboratory is used.
• Section 11.3.2	• ~~Progesterone~~ **Progestogen**-only hormonal contraception associated with inhibition of ovulation • ~~Progesterone~~ **Progestogen**-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action	Terminology was corrected.
• Section 11.4	The following changes were made: • Section 11.4.1 Definition of AE - Events to be Collected as AEs: **Lack of efficacy by itself 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 an AE or SAE if they fulfill the definition of an AE or SAE**. • The following was deleted from the explanation of hospitalization in Section 11.4.2. Definition of SAE - Requires inpatient hospitalization or prolongation of existing hospitalization "~~(usually involving at least an overnight stay)~~"	These changes to Appendix 4 for AEs/SAEs have been made to align the definitions with the current argenx protocol template.
• Section 11.4.4	• The following changes were made to Section 11.4.4. Reporting of SAEs and AESIs: SAE **and AESI** Reporting ~~via paper form~~:	These changes clarify the SAE and AESI reporting procedures.

Section(s)	Change	Rationale
	• All SAEs and AESIs (Section 9.6.2) will be recorded (within 24 hours) on the ~~paper SAE report form and the~~ AE form ~~in~~ **of** the eCRF. **SAEs will also be recorded on the paper SAE report form.** • The investigator or designated site staff ~~should check that~~ **will ensure** all entered data are consistent. • An alert email for the SAE **and AESI** report**s** ~~in~~ **on** the eCRF will ~~then~~ automatically be sent by email to the **sponsor or designee's** ~~SAE coordinator's~~ safety mailbox via the electronic data capture (EDC) system. • The paper SAE report form ~~should~~ **will** be faxed or emailed to the **sponsor's designee** ~~SAE coordinator~~ **(see the Serious Adverse Event Reporting details on the first page of this protocol).** ~~Contacts for SAE reporting can be found on the frontpage.~~	
• Appendix 12	• This Appendix with the Administrative Structure has been deleted	This information will be captured in the Trial Master File.
• Appendix 14	• An Appendix was added to provide the Country-Specific requirements	The specific requirements of certain countries were added in an Appendix of this global protocol to align with the new EU Clinical Trials Regulation.

TABLE OF CONTENTS

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol number: ARGX-113-1802	**Drug:** ARGX-113/efgartigimod
Title of the trial: A Phase 2 Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	
Number of patients (total): Approximately 360 patients aged 18 years and older are planned to be enrolled in Stage A.	
Investigator(s): Multicenter trial	
Site(s) and region(s): Approximately 140 sites globally	
Trial start (planned): 2019	**Clinical phase:** Phase 2

Objectives:

Stage A (open-label, efgartigimod PH20 SC; 4-12 weeks [+ 1 optional additional week])

Primary objective:

- To assess the activity of efgartigimod PH20 SC (efgartigimod co-formulated with recombinant human hyaluronidase PH20 **[**rHuPH20]) based on the percentage of patients classified as treatment responders.

Secondary objectives:

- To assess the time to clinical improvement.
- To determine the treatment effect of efgartigimod PH20 SC based on clinical functional assessments of motor function and muscle strength.
- To assess the short-term safety and tolerability of efgartigimod PH20 SC.
- To assess the pharmacokinetics (PK) of efgartigimod PH20 SC.
- To assess the pharmacodynamic (PD) effect of efgartigimod PH20 SC.
- To assess the immunogenicity of efgartigimod and rHuPH20.
- To assess the EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire (EQ-5D-5L).

Stage B (double-blind, randomized-withdrawal, efgartigimod PH20 SC or placebo; up to 48 weeks)

Primary objective:

- To determine the efficacy of efgartigimod PH20 SC compared to placebo based on the time needed for the occurrence of the first evidence of clinical deterioration.

Secondary objectives:

- To determine the efficacy of efgartigimod PH20 SC compared to placebo based on clinical functional assessments of disease disability and motor function and muscle strength.
- To assess the safety and tolerability of efgartigimod PH20 SC.
- To assess the PK of efgartigimod PH20 SC.
- To assess the PD effect of efgartigimod PH20 SC.
- To assess the immunogenicity of efgartigimod and rHuPH20.
- To assess the EQ-5D-5L.

Rationale

CIDP is considered an autoimmune disease. An unmet medical need exists for an efficacious treatment of CIDP with a favorable safety and tolerability profile and more convenient administration than that provided by current treatments. A weekly subcutaneous (SC) treatment option consisting of efgartigimod PH20 SC administered within a few minutes could offer clinically significant benefits to CIDP patients. In this trial, patients with CIDP will be administered efgartigimod PH20 SC at the dose of 1000 mg. This dose was well-tolerated in the prior

Phase 1 trial ARGX-113-1901 in healthy adult subjects and reduced immunoglobulins G (IgGs) to a level associated with clinical benefit in prior trials in patients with an autoimmune disease (ie, patients with generalized myasthenia gravis [gMG] and patients with primary immune thrombocytopenia [ITP]).
Investigational product, dose, and mode of administration: The investigational medicinal product (IMP) by trial stage will be as follows: Stage A: • 1000 mg efgartigimod PH20 SC Stage B: • 1000 mg efgartigimod PH20 SC, and • placebo (containing an equivalent amount of rHuPH20) SC
Methodology: This is a Phase 2, prospective, multicenter trial on the efficacy, safety, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC administered SC in patients aged 18 years and older with CIDP. This trial will be conducted in 2 stages: An open-label Stage A and a randomized-withdrawal, double-blind, placebo-controlled Stage B. During the screening period of a maximum of 28 days, diagnosis of CIDP will be confirmed by a CIDP confirmation committee (CCC), and overall eligibility will be confirmed by the medical monitor. Eligible patients receiving treatment for CIDP at screening will discontinue that treatment and enter the run-in period for up to 12 weeks until evidence of clinically meaningful deterioration (ECMD)[*] is confirmed (ie, observed during a trial visit), at which time eligible patients will enter Stage A at baseline (D1A). Eligible patients who are treatment-naïve or discontinued treatment with corticosteroids and/or intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) at least 6 months prior to screening (who are considered equal to treatment-naïve patients) will enter Stage A directly, if during screening documented evidence for worsening on the total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, further referred to as "adjusted INCAT score," within 3 months prior to screening is available compared to previous adjusted INCAT score within 6 months prior to screening. Patients eligible for Stage A will receive open-label IMP as weekly SC administrations of efgartigimod PH20 SC for up to 12 weeks (with optional 1 additional week for confirmation of evidence of clinical improvement [ECI[†]], if needed), with a minimum of 4 administrations. During Stage A, patients will be monitored for ECI.

[*] Evidence of clinically meaningful deterioration (ECMD) is defined as fulfilling of any of the following criteria during the run-in period only: 1) Adjusted INCAT score increase by ≥1 point from the first visit of the run-in period (RI-V1), and/or 2) I-RODS decrease by ≥4 points (using the centile metric) from RI-V1, and/or 3) Mean grip strength decrease by ≥8 kiloPascal (kPa) in 1 hand using the handheld vigorimeter from RI-V1.

[†] Evidence of clinical improvement (ECI) will be determined during Stage A is defined as follows:

For non-naïve patients:

Patients who deteriorate in adjusted INCAT score during the run-in period (increase ≥1 point versus the first visit of the run-in period [RI-V1]) can only be entered in Stage B if they show improvement in adjusted INCAT score during Stage A (decrease ≥1 point versus Stage A baseline [D1A]). These patients can enter Stage B at the time the improvement on the adjusted INCAT score is confirmed.

Patients who have no change in adjusted INCAT score during the run-in period can be entered in Stage B in the following cases:

- When improvement on the adjusted INCAT score (decrease ≥1 point) versus D1A is confirmed.
- When no change in adjusted INCAT score is observed during Stage A and:
  - When improvement during Stage A on I-RODS (increase ≥4 points versus D1A) is confirmed in case deterioration on only I-RODS (decrease ≥4 points) was observed during run-in.
  - When improvement during Stage A on grip strength (increase ≥8 kPa versus D1A) is confirmed in case deterioration on only grip strength (decrease ≥8 kPa) was observed during run-in.
  - When improvement during Stage A on either I-RODS (increase ≥4 points versus D1A) or grip strength (increase ≥8 kPa versus D1A) is confirmed in case deterioration was observed on both I-RODS (decrease ≥4 points) and grip strength (decrease ≥8 kPa) during run in.

For naïve patients:

Naïve patients, who did not enter the run-in period and who show an improvement during Stage A of at least 1 grade on the adjusted INCAT score (ie, decrease by ≥1 point) compared to D1A, can enter Stage B at the time the improvement on the adjusted INCAT score (decrease ≥1 point) is confirmed.

Patients who fulfilled the criteria for ECI at 2 consecutive visits (confirmed ECI status), will roll over to the randomized-withdrawal, placebo-controlled Stage B. Patients who do not have confirmed ECI are not eligible for Stage B and will end the trial after performing the safety follow-up visit 28 days after the last administration of the IMP.

After the first 30 patients have reached the end of Stage A, an interim analysis will be conducted on the proportion of patients with confirmed ECI using the exact (Clopper-Pearson) 90% 1-sided lower confidence interval (CI) for a go/no-go decision to continue the trial. During the interim analysis, the trial will continue without any interruption, neither for trial enrollment nor for visits or treatments of patients participating in any trial period.

Patient for whom ECI in Stage A has been confirmed, will enter the double-blind, randomized-withdrawal Stage B and will be randomized at Stage B baseline (D1B) in a 1:1 ratio to receive weekly IMP consisting of efgartigimod PH20 SC or placebo. The randomized-withdrawal Stage B will last for up to 48 weeks.

All patients randomized to the double-blind, randomized-withdrawal Stage B will be dosed with IMP weekly but will return to the clinic in 4-week intervals (every 4 weeks). Administration of randomized IMP treatment can only occur after completion of all indicated assessments. Patients will be discharged from the center if there are no safety concerns in the opinion of the investigator. In between the trial visits in Stage B, patients will be given the option to come to the trial center weekly for drug administration or will be provided with home nurse service for IMP injecting. Upon agreement with the investigator, site personnel, and the patient, the most suitable solution will be provided. Administration of IMP will occur always within a time window of ± 2 days with respect to the pre-planned date of administration.

Patients completing Week 48 and in the opinion of the investigator benefit from trial treatment at Week 48 or patients having an event of worsening on the adjusted INCAT score of 1 point or a worsening on the adjusted INCAT score of ≥2 points compared to Stage B baseline (for the latter, no confirmation is needed) will be allowed to roll over to the open-label extension (OLE) trial when they are receiving IMP. Patients completing Week 48 who will not roll over to the OLE trial as well as patients with an early discontinuation, will have a safety follow-up visit 28 days after the last IMP administration, will stop the trial, and will be treated as considered appropriate by the investigator.

When eighty-eight (88) events have been observed for the primary endpoint analysis of Stage B (see sample size section), then the trial will stop. In that case, patients in Stage A and Stage B will perform an early discontinuation visit and patients who are receiving IMP will be given the opportunity to continue efgartigimod PH20 SC treatment in the OLE trial. Additionally, at the time of the 88th event, patients in run-in will also be given the option to roll over to the OLE trial after performing an early discontinuation visit. Patients who will not roll over to the OLE trial, will attend a follow-up visit 28 days after the last IMP dose.

From Stage A onwards, patients will receive training for self-administration of IMP, which is foreseen in the OLE trial (not in the ARGX-113-1802 trial).

Inclusion and exclusion criteria:

Inclusion criteria:

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

1. Ability to understand the requirements of the trial, provide written informed consent (including consent for the use and disclosure of research-related health information), willingness and ability to comply with the trial protocol procedures (including required trial visits).
2. Male or female patient aged 18 years or older, at the time of signing the informed consent.
3. Diagnosed with probable or definite CIDP according to criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS, 2010),[2] progressing or relapsing forms.
4. CIDP Disease Activity Status (CDAS)[3] score ≥2 at screening.
5. An INCAT score ≥2 at the first run-in visit (RI-V1; for patients entering run-in) or Stage A baseline (A-V1; for treatment-naïve patients with documented evidence for worsening on the total adjusted INCAT disability score within 3 months prior to screening). Patients with an INCAT score of 2 at trial

entry must have this score exclusively from the leg disability score; for patients with an INCAT score of ≥3 at trial entry, there are no specific requirements for arm or leg scores.

6. Fulfilling any of the following treatment conditions:
   - Currently (ie, within the last 6 months) treated with pulsed corticosteroids, oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg, and the patient is willing to discontinue this treatment at the first run-in visit (RI-V1); OR
   - Without previous treatment (treatment-naïve); OR
   - Treatment with corticosteroids and/or IVIg or SCIg discontinued at least 6 months prior to screening.

   Note: *Patients not treated with monthly or daily corticosteroids, IVIg or SCIg for at least 6 months prior to screening are considered as equal to treatment-naïve patients.*
7. Women of childbearing potential who have a negative serum pregnancy test at screening and a negative urine pregnancy test up to Stage A baseline (D1A).

8.a. Women of childbearing potential must use an acceptable method of contraception from signing the ICF until the date of the last dose of IMP.

9. Inclusion criterion removed in protocol amendment 4.

Exclusion criteria:

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

1. Pure sensory atypical CIDP (EFNS/PNS definition).[2]
2. Polyneuropathy of other causes, including the following:
   - Multifocal motor neuropathy;
   - Monoclonal gammopathy of uncertain significance with anti-myelin-associated glycoprotein immunoglobulin M (IgM) antibodies;
   - Hereditary demyelinating neuropathy;
   - Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin change syndromes;
   - Lumbosacral radiculoplexus neuropathy;
   - Polyneuropathy most likely due to diabetes mellitus;
   - Polyneuropathy most likely due to systemic illnesses;
   - Drug- or toxin-induced polyneuropathy.
3. Any other disease that could better explain the patient's signs and symptoms.
4. Any history of myelopathy or evidence of central demyelination.
5. Current or past history (within 12 months of screening) of alcohol, drug or medication abuse.
6. 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 patient or could affect adherence with the trial protocol.

   Note: *At screening, suicidality will be assessed using the Columbia-suicide severity rating scale (C-SSRS); patients with a high suicide risk will be excluded from the trial (ie, patients 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 above 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.*
7. Patients with clinically significant active or chronic uncontrolled bacterial, viral, or fungal infection at screening, including patients who test positive for an active viral infection at screening with:
   - Active Hepatitis B Virus (HBV): serologic panel test results indicative of an active (acute or chronic) infection;
   - Active Hepatitis C Virus (HCV): serology positive for HCV-Ab;

- Human Immunodeficiency Virus (HIV) positive serology associated with an Acquired Immune Deficiency Syndrome (AIDS)-defining condition or with a cluster of differentiation 4 (CD4) count ≤200 cells/mm^3.

8. Total IgG level <6 g/L at screening.

9.a. Treatment with the following:

- **Within 3 months (or 5 half-lives of the drug, whichever is longer) before screening:** plasma exchange or immunoadsorption, any concomitant fragment crystallizable (Fc)-containing therapeutic agents or other biological, or any other investigational product;
- **Within 6 months before screening:** rituximab, alemtuzumab, any other monoclonal antibody, cyclophosphamide, interferon, tumor necrosis factor–alpha inhibitors, fingolimod, methotrexate, azathioprine, mycophenolate, any other immunomodulating or immunosuppressive medications, and oral daily corticosteroids >10 mg/day.

Note: *Patients using IVIg, SCIg, pulsed corticosteroids, and oral daily corticosteroids ≤10 mg/day can be included.*

- Patients who (intend to) use prohibited medications and therapies (see Section 7.4.2) during the trial.

10. a. Pregnant and lactating women and those intending to become pregnant during the trial.

11. Patients with any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of CIDP.

12.a. Patients who received a live-attenuated vaccine fewer than 28 days before screening. Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not exclusionary.

13. Patients who have a history of malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before the first IMP administration. Patients with the following cancer can be included anytime:
    - Adequately treated basal cell or squamous cell skin cancer,
    - Carcinoma in situ of the cervix,
    - Carcinoma in situ of the breast, or
    - Incidental histological finding of Prostate cancer (TNM [tumor, nodes, and metastases classification] stage T1a or T1b).

14. Patients who previously participated in a trial with efgartigimod and have received at least 1 administration of IMP.

15. Patients with known medical history of hypersensitivity to any of the ingredients of IMP.

16. Patients with clinical evidence of other significant serious disease or patients who underwent a recent or have a planned major surgery, or any other reason which could confound the results of the trial or put the patient at undue risk.

Maximum duration of patient involvement in the trial: After a screening period of up to 28 days and a run-in period up to 12 weeks, the total duration of IMP dosing is up to 61 weeks and includes 2 treatment stages: Stage A will be up to 12 weeks (with optional 1 additional week) open-label treatment of efgartigimod PH20 SC and Stage B will be up to 48 weeks of double-blind treatment with IMP (efgartigimod PH20 SC or placebo). Follow-up period for patients not rolling over into the extension trial or for patients who prematurely discontinue IMP, will be 28 days after the last dose of IMP.

The maximum total trial duration is 80 weeks with a maximum of 61 weeks on IMP:

- Screening period: up to 28 days
- Run-in period: up to 12 weeks (not required for treatment-naïve patients)
- Stage A: 4–12 weeks (with optional 1 additional week)
- Stage B: up to 48 weeks
- Follow-up period: 28 days after the last dose of IMP for patients who do not enroll into the OLE trial ARGX-113-1902.

Endpoints and statistical analysis

Populations for Analyses

Safety population: The Stage A safety population (SAF-A) will include all patients who received at least 1 dose of IMP in Stage A. The Stage B safety population (SAF-B) will include all patients who received at least 1 dose of IMP in Stage B.

Modified intent-to-treat (mITT) population: The mITT population will include all randomized patients who received at least 1 dose of IMP in Stage B.

Per protocol (PP) population: The PP population comprises all Stage B patients in the mITT population for whom no major protocol deviation was reported.

Note: Below the primary and secondary endpoints are listed of Stage A and Stage B. In addition, there are exploratory endpoints [redacted] that are described in the body text of the protocol.

Stage A

Primary endpoint: Percentage of patients with confirmed ECI.

Secondary endpoints:

- Evidence of clinical activity:
  - Time to initial confirmed ECI.
  - Change from Stage A baseline (D1A) over time in:
    - Adjusted INCAT score
    - Medical Research Council (MRC) sum score
    - 24-item Inflammatory Rasch-built Overall Disability Scale (I-RODS) disability scores
    - Timed Up and go (TUG) score
    - Mean grip strength assessed by Martin vigorimeter
- Safety:
  - Exposure adjusted occurrence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT);
  - Incidence of clinically significant laboratory abnormalities.
- PK profile:
  - Pre-dosing efgartigimod serum concentrations over time during Stage A.
- PD profile:
  - Changes of serum IgG levels (total IgG) over time during Stage A.
- Immunogenicity:
  - Percentage of patients with and titers of binding antibodies (BAb) toward efgartigimod and/or rHuPH20 during Stage A.
  - Presence of neutralizing antibodies (NAb) against efgartigimod and titers of NAb against rHuPH20 during Stage A.
- PRO:
  - Changes from D1A in EQ-5D-5L over time during Stage A.

Stage B

Primary Endpoint:

- Time to first adjusted INCAT deterioration compared to Stage B baseline.

  ***Note*:** Time to first adjusted INCAT deterioration is defined by the time from first dose of double-blind IMP to the first adjusted INCAT score increase of 1 point compared to Stage B baseline, if the deterioration is confirmed at a consecutive visit 3-7 days after the first adjusted INCAT score increase of 1 point. For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required.

Secondary Endpoints:

- Clinical Efficacy:
  - Time to CIDP disease progression.
    ***Note*:** Time to CIDP disease progression is defined by the time from first dose of double-blind IMP to the first I-RODS score decrease ≥4 points compared to Stage B baseline using the centile metric.
  - Percentage of patients with improved functional level compared to Stage B baseline as measured by an increase in the 24-item I-RODS score up to Week 48.
  - Change from Stage B baseline over time in:
    - Adjusted INCAT score
    - MRC Sum score
    - 24-item I-RODS disability scores
    - TUG score
    - Mean grip strength assessed by Martin vigorimeter
  - Time to 10% decrease in the 24-item I-RODS during Stage B.
- Safety:
  - Incidence of TEAEs and SAEs by SOC and PT during Stage B.
  - Incidence of clinically significant laboratory abnormalities during Stage B.
- PK Profile:
  - Pre-dosing efgartigimod serum concentrations over time during Stage B.
- PD Profile:
  - Changes of serum IgG levels (total IgG) over time during Stage B.
- Immunogenicity:
  - Percentage of patients with and titers of BAb toward efgartigimod and/or rHuPH20 during Stage B.
  - Presence of NAb against efgartigimod and titers of NAb against rHuPH20 during Stage B.
- PRO:
  - Changes from Stage B baseline in EQ-5D-5L over time during Stage B.

Hypothesis:

Stage A

- For the interim analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact Clopper-Pearson 90% 1-sided lower CI. For the final analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact Clopper-Pearson 2-sided 95% CI.

Stage B

- Null hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is 1 (ie, hazard ratio = 1).
- Alternative hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is ≠1 (ie, hazard ratio ≠1).

Stage A and Stage B testing will be on different populations and hence are not considered to be multiple comparisons. Therefore, no adjustment for multiplicity will be made.

Primary Efficacy Analyses:

The primary endpoint of time to an adjusted INCAT deterioration compared to Stage B baseline will be analyzed via Cox regression modeling in the mITT population. Patients without adjusted INCAT deterioration will be censored at week 48. The analysis will be stratified for randomization stratification factors (ie, according to their prior CIDP medication and the adjusted INCAT score during Stage A). A fixed effect term will be included as a covariate for randomized treatment. The hazard ratio will be estimated from the model along with the associated 95% CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and median times will be estimated.

Secondary Efficacy Analyses

The time to CIDP disease progression during Stage B up to week 48, defined by I-RODS deterioration of ≥4 points compared to Stage B baseline, will be analyzed in the same fashion as the primary endpoint.

The percentage of patients with improved functional level (compared to Stage B baseline) as measured by the I-RODS score during Stage B up to week 48 will be analyzed by exact logistic regression. A fixed effect term will be included for randomized treatment and Stage B baseline I-RODS score will be included as a covariate. The odds ratio will be estimated from the model along with the associated 95% CI and 2-sided p-value. Exact Clopper-Pearson 2-sided 95% CI limits will be calculated for the proportion of patients with disease progression in each arm.

The change from Stage B baseline over time in clinical functional assessments of motor function and muscle strength and PROs will be summarized descriptively in addition to the analysis for time to 10% decrease in 24-item I-RODS.

PRO: EQ-5D-5L Analysis

EQ-5D-5L scores and changes from baseline (ie, changes from D1A over time during Stage A and changes from Stage B baseline over time during Stage B) will be presented using standard summary statistics.

Safety Analyses

Summaries of adverse events (AEs) and other safety parameters will be provided for Stage A (SAF-A), Stage B (SAF-B) (by treatment arm), and Stage A and Stage B combined (SAF-A and SAF-B) (for efgartigimod PH20 SC treatment).

AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. AEs reported from the first dose of IMP until 30 days after the last dose of IMP will be considered as TEAEs and will be summarized descriptively. TEAEs and Adverse Events of Special Interest (AESIs) will be listed corresponding to SOC and MedDRA PT. Multiple occurrences of a single PT in a patient will only be counted once at the maximum severity/grade. The severity will be assessed using the common terminology criteria for AEs (CTCAE). All AEs will be summarized by relatedness to IMP. Any AEs leading to death or discontinuation of IMP will also be summarized. Clinically significant laboratory abnormalities will be summarized descriptively.

PK, PD, and Immunogenicity Analysis

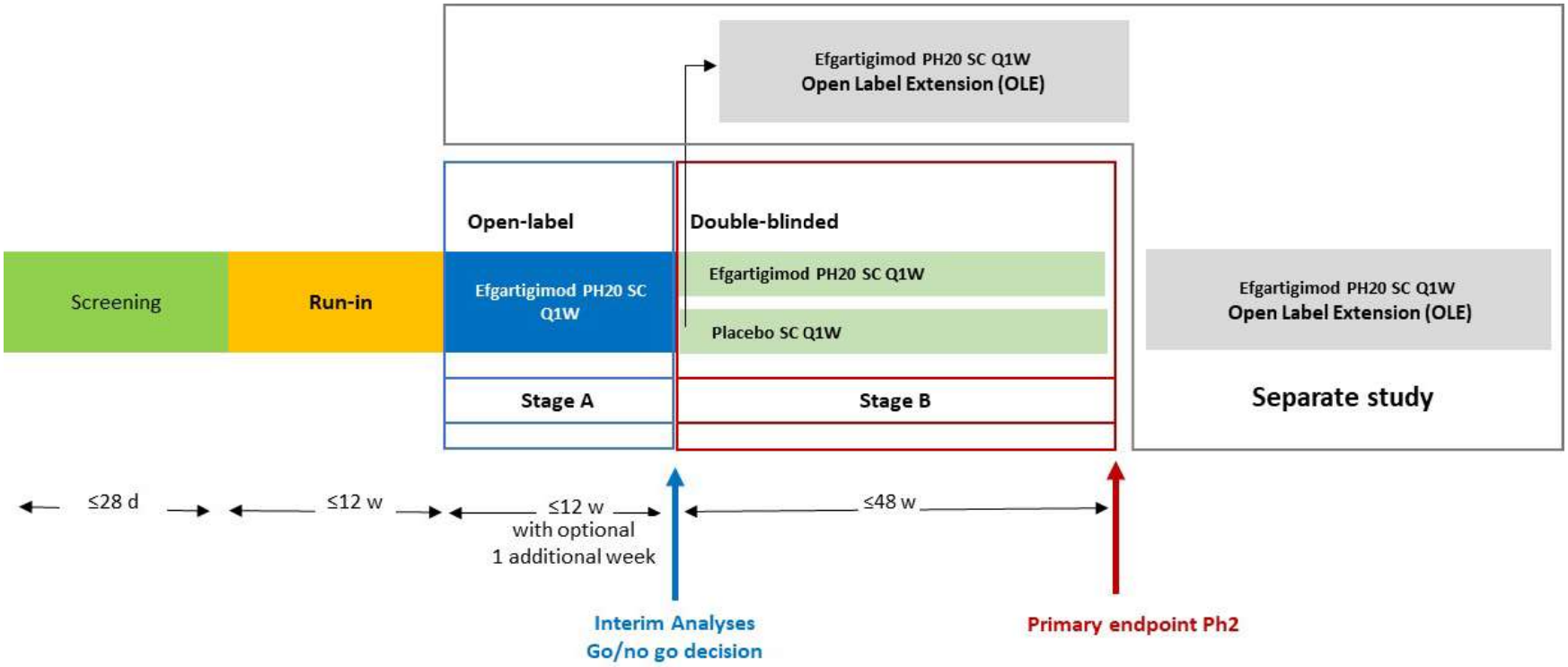
PK, PD, and immunogenicity parameters will be summarized descriptively.

Sample Size Considerations:

If it is hypothesized that the event rate of efgartigimod PH20 SC compared to placebo is 0.50 (ie, hazard ratio of 0.50), then 88 events are required to provide 90% power at a 1-sided alpha level of 0.025 using a log-rank test. An event is defined as an adjusted INCAT increase during Stage B. The events will be monitored in a blinded way to ensure the trial is sufficiently powered. The expected sample size assumes a 48-week maximum follow-up period for each patient, an accrual rate of 4 patients per month during the first 6 months and an accrual rate of 7.8 patients per month thereafter. To obtain a sufficient number of patients randomized into Stage B, up to approximately 360 patients would be required to be enrolled into Stage A. Patients will continue to be randomized into Stage B until 88 events are observed as per the sample size calculation, the trial will end when the 88th event is observed.

Date of Protocol: 12 Oct 2022

1.2. Schema



Abbreviations: d = day; efgartigimod PH20 SC = efgartigimod with rHuPH20 (co-formulation) for SC administration; OLE=open-label extension; placebo = placebo with rHuPH20; Q1W = once a week; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous(ly); q1w=once weekly; w = week.
Note: Patients who show ECI only at the last visit of the 12-weeks Stage A period may be allowed to extend Stage A for a further week with 1 additional consecutive visit in order to get ECI confirmed at a consecutive visit. Only patients with confirmed ECI will be randomized and receive double-blind IMP in Stage B.
Note: Approximately 360 patients aged 18 years and older are planned to be enrolled in Stage A.
Note: After the first 30 patients have reached the end of Stage A, an interim analysis will be conducted on the proportion of patients with confirmed ECI for a go/no-go decision to continue the trial.

1.3. Schedule of Activities (SoA)

1.3.1. SoA for Screening, Run-in, and Stage A

	Screening[a] ≤28 days	Run-in Period ≤12 weeks[b]		Stage A: Open-Label Period ≤12 Weeks (With Optional 1 Additional Week)[c]													Unsche-duled[e]	Safety Follow-up[f]
		RI-V1	RI-V2 to RI-V4	A-V1	A-V2	A-V3	A-V4	A-V5	A-V6[c]	A-V7[c]	A-V8[c]	A-V9[c]	A-V10[c]	A-V11[c]	A-V12[c]	A-V13[c] (Addi-tional)	EOSA/ ED[d]	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D8	D15	D22	D29	D36[c]	D43[c]	D50[c]	D57[c]	D64[c]	D71[c]	D78[c]	D85			
Assessment/Procedure		±0 days	±2 days	±0 days	±2 days														
Informed consent	●																		
Demographics	●																		
In-/exclusion criteria	●	●		●															
Medical history[g]	●																		
12-lead ECGs	●			●													●	●	●
CDAS	●																		
Physical exam and vital signs	●[h]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]	●[i]
Pregnancy test	●[j]	●[k]	●[k]	●[k]				●[k]				●[k]					●[k]	●[k]	●[k]
Adjusted INCAT score		●	●	●	●	●	●	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	●	●	
MRC Sum score		●	●	●	●	●	●	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	●	●	
I-RODS score		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Mean grip strength		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
TUG test		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
EQ-5D-5L				●													●	●	
[redacted]				●													●	●	
[redacted]		●[m]															●	●	
[redacted]				●													●	●	

	Screening[a] ≤28 days	Run-in Period ≤12 weeks[b]		Stage A: Open-Label Period ≤12 Weeks (With Optional 1 Additional Week)[c]														Unsche-duled[e]	Safety Follow-up[f]
		RI-V1	RI-V2 to RI-V4	A-V1	A-V2	A-V3	A-V4	A-V5	A-V6[c]	A-V7[c]	A-V8[c]	A-V9[c]	A-V10[c]	A-V11[c]	A-V12[c]	A-V13[c] (Addi-tional)	EOSA/ ED[d]	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D8	D15	D22	D29	D36[c]	D43[c]	D50[c]	D57[c]	D64[c]	D71[c]	D78[c]	D85			
Assessment/Procedure		±0 days	±2 days	±0 days	±2 days														
[redacted]				●													●	●	
[redacted]					●												●	●	
Suicidality assessment[n]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood & urine clinical laboratory safety tests	●[o]			●	●	●	●	●									●	●	●
HIV, HBV, HCV, and tuberculosis testing	●																	●[p]	
Blood sampling for PK and PD analysis[q]				●[w]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for immunogenicity analysis[r]	●[w]			●[w]		●		●				●					●	●	●
[redacted]		●[w]		●[w]													●	●	
IMP self-administration training[t]				●	●	●	●	●[t]	●[t]	●[t]	●[t]	●[t]	●[t]	●[t]	●[t]	●[t]			
IMP administration (SC)[u]				●	●	●	●	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]			
IMP accountability[u]				●	●	●	●	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●		
Adverse events[v]	‹----------●																	----------›	
Concomitant therapies[g,v]	‹----------●																	----------›	

Footnotes are on next page

ADA=anti-drug antibodies; AE=adverse event; [redacted]; CDAS=CIDP disease activity status; CIDP=chronic inflammatory demyelinating polyneuropathy; D1A=baseline of Stage A; D1B=baseline of Stage B; ECG=electrocardiogram; ECI=evidence of clinical improvement; ECMD=evidence of clinically meaningful deterioration; ED=early discontinuation; EOSA=end of Stage A; EQ-5D-5L=EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire; [redacted] HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; IgG=immunoglobulin G; IMP=investigational medical product; INCAT=inflammatory neuropathy cause and treatment; I-RODS=Inflammatory-Rasch-built Overall Disability Scale; OLE=open-label extension; PD=pharmacodynamic(s); [redacted] PK=pharmacokinetic(s); rHuPH20=recombinant human hyaluronidase PH20; [redacted]; MRC=Medical Research Council; SAE=serious adverse event; SC=subcutaneous(ly); [redacted] TUG=timed up and go; UNS=unscheduled; V=visit; W=week.

a. Within 28 days before the first day of run-in (visit RI-1). If needed a medical monitor can authorize the extension of the screening period. For treatment-naïve patients screening can occur within 28 days before D1A, if during screening documented evidence for worsening on the adjusted INCAT score within 3 months prior to screening is available compared to previous adjusted INCAT score within 6 months prior to screening.

b. Site visit every 4 weeks. R1-V1: day 1 of run-in; R1-V2:run-in week 4 (±2 days); R1-V3: run-in week 8 (±2 days), and R1-V4: run-in week 12 (±2 days). A patient showing ECMD will enter Stage A immediately. Patients will receive appropriate training and instructions to assess every week the disability status by means of I-RODS and grip strength. If the patient does not have evidence of ECMD by the end of the run-in period, then he/she should be recorded as a run-in failure.

c. Weekly administration of efgartigimod PH20 SC (±2 days). Patients, who show ECI only after the 12th IMP administration (ie, 1 week after the A-V12 visit), may be allowed to extend Stage A for a further week with an additional visit (the visit at which ECI is observed for the first time will then be A-V13) and patients will need to come back 1 week later (ie, 1 week after A-V13) to confirm ECI.
All patients with confirmed ECI following a minimum of 4 IMP administrations will have an EOSA visit and will enter Stage B. If the patient does not show confirmed ECI during Stage A, then he/she will have an EOSA visit and end the trial after a follow-up visit 28 days after the last administration of IMP.

d. The assessments in this visit are for patients who end Stage A (ie, EOSA visit; for patients with or without confirmed ECI) as well as for patients who discontinue the trial prematurely (ie, ED visit). Patients with confirmed ECI can continue the trial in Stage B (in this case, the patients will have a combination of the EOSA visit and the Baseline Stage B [D1B] visit [see Section 1.3.2]).

   Note: Patients who end Stage A with confirmed ECI and will go to Stage B, should have had at least 4 IMP administrations during Stage A.

   Note: Patients with ECI only after 12 IMP administrations in Stage A, may be allowed to extend Stage A for 1 more week (in order to determine if ECI is confirmed or not) with an additional consecutive visit (see footnote above).

e. The investigator can decide which of the assessments need to be performed at each unscheduled visit (refer to Section 5.1.5).

f. Only applicable for patients who do not continue in Stage B and for patients who prematurely discontinued IMP in case IMP was stopped less than 28 days before the last trial visit.

g. At screening, all available vaccination history will be captured as part of prior medication. For vaccines where multiple doses or boosters are received, only the most recent one must be recorded. Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.

   Note: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.

h. Includes physical examination, height, weight, semi-supine blood pressure and heart rate, and body temperature.

i. Includes physical examination, weight, semi-supine blood pressure and heart rate, and body temperature.

j. A serum pregnancy test will be conducted at screening.

k. Urine pregnancy tests will be conducted every 4 weeks during the trial and at the follow-up visit.

l. These tests are only required for confirmation of improvement (for patients with improvement in the previous visit).

[redacted]

n. At screening, suicidality will be assessed with the Columbia-suicide severity rating scale (C-SSRS) (see Section 9.2). During the trial, suicidality will be assessed by specifically answering 1 question from the PHQ-9 depression questionnaire (see Section 9.15).

o. At screening, total IgG will be measured (by central laboratory as part of the blood chemistry tests) to determine eligibility.

p. Serology can be retested only during the screening period.

q. For PK, pre-dose (within 2 hours prior to start of IMP administration at the trial visits) samples will be taken. At these time points, blood samples will also be taken for PD analysis. PD analysis includes the measurement of total IgG. IgG testing must not be performed locally.

r. Blood samples for immunogenicity testing will be taken pre-dose at the trial visits to measure ADA against efgartigimod (measured in serum) and antibodies against rHuPH20 (measured in plasma).

s. Optional blood samples will be taken for autoantibodies testing (serum) and serum-sample storage for future testing.

t. Patients will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1802 trial) during the first 4 visits when IMP is administered; thereafter, training for self-administration is optional (only if needed).

u. IMP will be administered weekly at the site in Stage A (IMP administration will be after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses and after all assessments needed for determination of ECI). Patients will receive a minimum of 4 IMP administrations in Stage A. Note that IMP in Stage A will **not** be administered if ECI is confirmed at the visit (and the patient has received at least 4 IMP administrations). When ECI is confirmed (ie, ECI observed at the second consecutive visit), the patient will be randomized and receive the first double-blind IMP administration in Stage B (ie, the visit at which ECI is confirmed will be a combination of the EOSA visit and the Stage B baseline [D1B] visit [see Section 1.3.2]).

v. AEs and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity. In case of early discontinuation, any AEs/SAEs should be assessed for 30 days following the ED visit or until satisfactory resolution or stabilization.

w. Blood samples may also be used to cross-validate the PK, PD, biomarker, and ADA assays in CIDP matrix (serum and plasma).

1.3.2. SoA for Stage B and Follow-up

	Stage B: Randomized-Withdrawal Treatment ≤48 Weeks													UNS	Safety Follow-up[d]
	B-V1	B-V2	B-V3	B-V4	B-V5	B-V6	B-V7	B-V8	B-V9	B-V10	B-V11	B-V12	B-V13	UNS V[c]	28 (±3) Days After Last IMP Dose
	D1B[a]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ED[b]		
Assessment/Procedure	±0 days	±2 days													
Randomization	●														
12-lead ECGs	●			●			●			●			●	●	●
Physical exam and vital signs[e]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Pregnancy test[f]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adjusted INCAT score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
MRC sum score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	

	Stage B: Randomized-Withdrawal Treatment ≤48 Weeks													UNS	Safety Follow-up[d]
	B-V1	B-V2	B-V3	B-V4	B-V5	B-V6	B-V7	B-V8	B-V9	B-V10	B-V11	B-V12	B-V13	UNS V[c]	28 (±3) Days After Last IMP Dose
	D1B[a]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ED[b]		
Assessment/Procedure	±0 days	±2 days													
I-RODS score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Mean grip strength	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
TUG test	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
EQ-5D-5L	●			●			●			●			●	●	
[redacted]	●			●			●			●			●	●	
[redacted]	●			●			●			●			●	●	
[redacted]	●			●			●			●			●	●	
[redacted]	●			●			●			●			●	●	
[redacted]													●	●	
Suicidality assessment	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood & urine safety tests	●			●			●			●			●	●	●
Blood sampling for PK and PD analysis[g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood sampling for immunogenicity analysis[h]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
[redacted]	●			●			●			●			●	●	
IMP self-administration training[j]	●	●	●	●	●	●	●	●	●	●	●	●			
IMP administration (SC)[k]	●	●	●	●	●	●	●	●	●	●	●	●[k]			
IMP dispensation	●	●	●	●	●	●	●	●	●	●	●	●[k]			
IMP accountability	●	●	●	●	●	●	●	●	●	●	●	●	●		
Adverse events[l]	‹----------●														----------›
Concomitant therapies[l,m]	‹----------●														----------›

	Stage B: Randomized-Withdrawal Treatment ≤48 Weeks													UNS	Safety Follow-up[d]
	B-V1	B-V2	B-V3	B-V4	B-V5	B-V6	B-V7	B-V8	B-V9	B-V10	B-V11	B-V12	B-V13	UNS V[c]	28 (±3) Days After Last IMP Dose
	D1B[a]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ED[b]		
Assessment/Procedure	±0 days	±2 days													

ADA=anti-drug antibody; AE=adverse event; [redacted]; D1B=baseline of Stage B; ECG=electrocardiogram; ECI=evidence of clinical improvement; ED=early discontinuation; EQ-5D-5L=EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire; [redacted] Scale; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; IgG=immunoglobulin G; IMP=investigational medical product; INCAT=inflammatory neuropathy cause and treatment; I-RODS=Inflammatory-Rasch-built Overall Disability Scale; OLE=open-label extension; PD=pharmacodynamic(s); [redacted]; PK=pharmacokinetic(s); rHuPH20 = recombinant human hyaluronidase PH20; [redacted]; MRC=Medical Research Council; SAE=serious adverse event; SC = subcutaneous(ly); [redacted]; TUG=timed up and go; UNS=unscheduled; V=visit; W=week.

a. D1B will occur at the same visit, at which ECI has been confirmed in Stage A. There is no need to schedule an additional visit for D1B. All assessments are performed prior to IMP administration.

b. The assessments in this visit are for patients who end Stage B as well as for patients who discontinue the trial prematurely (ie, ED visit). Patients who will roll over to the open-label extension trial, will have a combination this last visit in the ARGX-113-1802 trial and the first visit of the open-label extension trial ARGX-113-1902.

c. The investigator can decide which of the indicated assessments need to be performed at each unscheduled visit (refer to Section 5.1.5).

d. This visit is not applicable for patients who roll over to the open-label extension trial and for patients who prematurely discontinued IMP in case IMP was stopped less than 28 days before the last trial visit.

e. Includes physical examination, weight, semi-supine blood pressure and heart rate, and body temperature.

f. Urine pregnancy test every 4 weeks and at the follow-up visit.

g. For PK, pre-dose (within 2 hours prior to start of IMP administration at the trial visits) samples will be taken. At these time points, blood samples will also be taken for PD analysis. PD analysis includes the measurement of total IgG. IgG testing must not be performed locally.

h. Blood samples for immunogenicity testing will be taken pre-dose at the trial visits to measure ADA against efgartigimod (measured in serum) and antibodies against rHuPH20 (measured in plasma).

i. Optional blood samples will be taken for autoantibodies testing (serum) and serum-sample storage for future testing.

j. Patients will be trained (refreshment training), if needed, to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1802 trial).

k. IMP will be administered at the site at the scheduled visits. This will be after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses. For IMP administrations between the scheduled visits, the patient can choose between nurse home visits or return to the trial site for the SC injection only. The last planned IMP administration is at week 47.

l. AEs and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity. In case of early discontinuation, any AEs/SAEs should be assessed for 30 days following the ED visit or until satisfactory resolution or stabilization.

m. Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.

Note: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.

2. ABBREVIATIONS AND DEFINITIONS OF TERMS

2.1. Abbreviations

Abbreviation	Expansion/Definition
21 CFR	Title 21 of the Code of Federal Regulations
Ab	Antibody
AChR-Ab	anti-acetylcholine receptor antibody
Ag	Antigen
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AIDS	Acquired Immune Deficiency Syndrome
ASCT	autologous stem cell transplant
BAb	binding antibodies
[redacted]	[redacted]
CCC	CIDP confirmation committee
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CDAS	CIDP disease activity status
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRO	contract research organization
C-SSRS	Columbia-suicide severity rating scale
CTCAE	common terminology criteria for adverse events
CTR	clinical trial report
D1A	baseline of stage A
D1B	baseline of stage B
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECI	evidence of clinical improvement
ECMD	evidence of clinically meaningful deterioration
eCRF	electronic case report form
ED	early discontinuation
efgartigimod PH20 SC	efgartigimod co-formulated with rHuPH20 for SC administration
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society

EOSA	end of Stage A
EQ-5D-5L	EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire
EU	European Union
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
[redacted]	[redacted]
GBS	Guillain-Barré syndrome
GCP	good clinical practice
gMG	generalized myasthenia gravis
[redacted]	[redacted]
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committees
Ig	Immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
INCAT	inflammatory neuropathy cause and treatment
IRB	Institutional Review Board
I-RODS	Inflammatory-Rasch-built Overall Disability Scale
IRR	infusion-related reaction
IRT	interactive response technology
ITP	immune thrombocytopenia
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
LDL	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities

MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGUSP	gammopathy-related polyneuropathy
mITT	modified intent-to-treat
MRC	Medical Research Council
NAb	neutralizing antibodies
NCI	National Cancer Institute
OLE	open-label extension
PD	pharmacodynamic(s)
[redacted]	[redacted]
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PP	per protocol
PRO	patient-reported outcome
PT	preferred term
OLE	open-label extension
QTcF	Fridericia corrected QT interval
rHuPH20	recombinant human hyaluronidase PH20
[redacted]	[redacted]
SAE	serious adverse event
SAF-A	Stage A safety population
SAF-B	Stage B safety population
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCIg	subcutaneous immunoglobulin
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TUG	timed up-and-go
Unsch	Unscheduled
US	United States
V	Visit
W	week
WHO	World Health Organization

2.2. Definitions of Terms

Evidence of clinically meaningful deterioration during the run-in period, evidence of clinical improvement during Stage A, and adjusted INCAT deterioration during Stage B are defined as follows:

Term	Definition
ECMD	Evidence of clinically meaningful deterioration (ECMD) is defined as the fulfilling of any of the following criteria during the run-in period only: • Total adjusted INCAT score increase by ≥1 point from the first visit of the run-in period (RI-V1), (Section 9.4.1), and/or • I-RODS decrease by ≥4 points (using the centile metric) from RI-V1 (Section 9.4.3), and/or • Mean grip strength decrease by ≥8 kPa in 1 hand using the handheld vigorimeter from RI-V1 (Section 9.4.4). ***Note**: Any patient showing ECMD at the trial site during the run-in period will enter Stage A immediately.*

ECI	For non-naïve patients:
	Patients who deteriorate in adjusted INCAT score during the run-in period (increase ≥1 point versus the first visit of the run-in period [RI-V1]) can only be entered in Stage B if they show improvement in adjusted INCAT score during Stage A (decrease ≥1 point versus Stage A baseline [D1A]). These patients can enter Stage B at the time the improvement on the adjusted INCAT score is confirmed.
	Patients who have no change in adjusted INCAT score during the run-in period and deteriorated on I-RODS and/or grip strength during run-in can be entered in Stage B in the following cases:
	• When improvement on the adjusted INCAT score (decrease ≥1 point) versus D1A is confirmed.
	• When no change in adjusted INCAT score is observed during Stage A and:
	  ○ When improvement during Stage A on I-RODS (increase ≥4 points versus D1A) is confirmed in case deterioration on only I-RODS (decrease ≥4 points) was observed during run-in.
	  ○ When improvement during Stage A on grip strength (increase ≥8 kPa versus D1A) is confirmed in case deterioration on only grip strength (decrease ≥8 kPa) was observed during run-in.
	  ○ When improvement during Stage A on either I-RODS (increase ≥4 points versus D1A) or grip strength (increase ≥8 kPa versus D1A) is confirmed in case deterioration was observed on both I-RODS (decrease ≥4 points) and grip strength (decrease ≥8 kPa) during run-in.
	For naïve patients:
	Naïve patients, who did not enter the run-in period and who show an improvement during Stage A of at least 1 grade on the adjusted INCAT score (ie, decrease by ≥1 point) compared to D1A, can enter Stage B at the time the improvement on the adjusted INCAT score (decrease ≥1 point) is confirmed.

Adjusted INCAT deterioration	A deterioration of the adjusted INCAT score is defined as an increase (ie, worsening) of 1 point on the adjusted INCAT score compared to Stage B baseline which is confirmed at a consecutive visit 3-7 days after the first adjusted INCAT score increase of 1 point. For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required.

D1A = baseline of Stage A; ECI = evidence of clinical improvement; ECMD = evidence of clinically meaningful deterioration; I-RODS = Inflammatory Rasch-built Overall Disability Scale; INCAT = Inflammatory Neuropathy Cause and Treatment

Investigational medicinal product in Stage A and Stage B is defined as follows:

Term	Definition
IMP	Investigational medicinal product by trial stage: • IMP in Stage A is efgartigimod PH20 SC. • IMP in Stage B is efgartigimod PH20 SC and placebo SC (containing an equivalent amount of rHuPH20).

Efgartigimod PH20 SC = efgartigimod co-formulated with rHuPH20 for SC administration; IMP = investigational medicinal product; rHuPH20= recombinant human hyaluronidase PH20; SC = subcutaneous(ly).

3. INTRODUCTION

3.1. Trial Rationale

The term chronic inflammatory demyelinating polyneuropathy (CIDP) has been used to identify a chronically progressive or relapsing symmetric sensorimotor disorder with cytoalbuminologic dissociation and interstitial and perivascular endoneurial infiltration by lymphocytes and macrophages. A number of variants of CIDP have been described that have immune or inflammatory aspects and electrophysiologic and/or pathologic evidence of demyelination in common. No consensus exists on the best approach to the nomenclature of these disorders. CIDP variants include disorders with predominantly sensory symptoms, distal symmetric disorder (DADS), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) also known as Lewis-Sumner syndrome, and CIDP with associated central nervous system (CNS) demyelination or with other systemic disorders.[4,5]

CIDP most commonly has an insidious onset with either a chronic progressive or a relapsing course. Occasionally, complete remission occurs. The estimated prevalence of CIDP is 1.8–8.9 per 100000.[6] CIDP may occur at any age, but it is more common in the fifth and sixth decades. A relapsing course is associated with younger age of patients (third and fourth decades).

The most common treatments are currently immunosuppressive or immunomodulatory interventions. These agents include intravenous immunoglobulin (IVIg) subcutaneous immunoglobulin (SCIg), plasmapheresis, prednisone, azathioprine, methotrexate, mycophenolate, cyclosporine, and cyclophosphamide. Their use is based on the proposed pathogenesis of CIDP as an immune-mediated condition, though for some of these agents, there is no clear evidence of a beneficial treatment effect.

However, an unmet medical need exists for an efficacious treatment of CIDP with a more specific mechanism of action maintaining quality of life (QoL) at the highest levels for the longest period possible, a favorable safety and tolerability profile, and more convenient administration that has a significantly lower impact on daily routines than that provided by current treatments.

While the abiding theory of CIDP pathogenesis is that cell-mediated and humoral mechanisms act together in an aberrant immune response to cause damage to peripheral nerves, the relative contributions of T cell and autoantibody responses remain largely undefined, though the role of humoral immune responses in these disorders has been emphasized.[7] However, there are several lines of evidence to support the conclusion that CIDP is an autoimmune disease mediated by humoral and/or cellular immunity against yet undefined Schwann cell/myelin antigens.[8]

Both sera and immunoglobulin G (IgG) molecules from patients with CIDP induce peripheral demyelination in susceptible animals and inhibit nerve conduction in several models of peripheral neuropathies.[9]

The autoimmune etiology is supported by the efficacy of treatments that target the immune system, including IVIg, plasma exchange and corticosteroids, and by evidence of an inflammatory response in the blood and peripheral nerves. Importantly, depletion of serum IgGs from CIDP patients showed promising efficacy in small scale trials.[10]

Critically, there is now evidence to suggest that nodal antigens are important in some cases of CIDP. Devaux et al. (2012)[11] found that 30% of patients with CIDP have serum IgG that binds to either the nodes of Ranvier or the paranodes in teased nerve fibers and in some cases identified the target antigens as neurofascin, gliomedin or contactin. Further, several trials have specifically identified autoantibodies against cell adhesion molecules at the nodes of Ranvier and paranodal regions in patients with CIDP.[7]

While further work is needed to examine the pathophysiological significance of nodal antigenic targets in CIDP, any disruption of nodal function is likely to interfere with normal nerve excitability and membrane potentials, contributing to conduction failure by interfering with saltatory conduction and ion channel function. In support of this, axonal excitability trials in patients with CIDP have revealed a range of findings demonstrating aberrant membrane excitability and membrane potential.[7]

It has been shown recently that the fragment crystallizable (Fc) gamma receptor (FcγR) regulatory system is disturbed in patients with CIDP.[9] Balancing activating vs inhibitory FcγR expression might provide a clinical benefit for patients with CIDP.

A subcutaneous (SC) treatment option consisting of efgartigimod with recombinant human hyaluronidase PH20 (rHuPH20) could offer clinically significant benefits to CIDP patients.

3.2. Background

Efgartigimod (ARGX-113) is a human immunoglobulin (Ig) G1-derived Fc of the za allotype that binds with nanomolar affinity to human neonatal Fc receptor (FcRn). Efgartigimod encompasses IgG1 residues D221-K447 (European Union [EU] numbering scheme) and has been modified with the so-called ABDEG™ technology (ABDEG™ = antibody that enhances IgG degradation)[12] to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of efgartigimod at both acidic and physiological pH results in a blockage of FcRn-mediated recycling of IgGs.

Given the essential role of the FcRn receptor in IgG homeostasis, inhibiting this FcRn function, as is achieved by efgartigimod, leads to rapid degradation of all IgGs, including disease-associated autoantibodies of the IgG isotype. This approach is thought to result in alleviation of signs and symptoms in IgG-driven autoimmune diseases.

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) administrations of efgartigimod have been investigated in the first-in-human trial ARGX-113-1501 in healthy adult subjects. A second trial ARGX-113-1702 in healthy adult subjects investigated the bioavailability, safety, tolerability, immunogenicity, PK, and PD following SC administration of efgartigimod and evaluated the reduction of the IV infusion time from 2 hours to 1 hour.

Phase 2 trials in immune thrombocytopenia (ITP; ARGX-113-1603) and myasthenia gravis (MG; ARGX-113-1602) have indicated that efgartigimod administered by IV infusion is well-tolerated, induces a specific, rapid PD effect (ie, reduction in IgG levels, including autoantibody levels), and is associated with improvement in clinical signs and symptoms in patients with ITP and MG, separately.[13] Additionally, the safety and tolerability of efgartigimod has been evaluated for the treatment of patients with pemphigus in the Phase 2 trial ARGX-113-1701 and for the treatment of patients with MG in the Phase 3 trial ARGX-113-1704.

For this Phase 2 trial in patients with CIDP, a fixed dose of efgartigimod PH20 SC was selected based on the results of the Phase 1 trial ARGX-113-1901 in healthy subjects that achieved a similar pharmacodynamic effect as that observed in generalized myasthenia gravis (gMG) and ITP, ie, IgG reduction, at steady state as achieved by weekly 10 mg/kg IV infusions. Doses of 10 mg/kg efgartigimod IV have demonstrated a favorable safety and efficacy profile across Phase 2 trials in MG and ITP patients. To select the fixed SC dose, an open-label, parallel group trial in healthy male subjects (ARGX-113-1901) has been performed to investigate the PK, PD, safety, and tolerability of different single fixed SC dose levels of efgartigimod co-administered with rHuPH20.

In the current trial, efgartigimod is co-formulated with the permeation enhancer rHuPH20 (efgartigimod PH20 SC). rHuPH20 acts as a spreading factor that increases the dispersion and absorption of other co-administered drugs and allows SC dosing of greater volumes than without rHuPH20. SC injections of rHuPH20 with fluids, small molecules, peptides, and proteins (eg, IgG) were well-tolerated in all clinical trial populations studied to date.[14]

3.3. Benefit/Risk Assessment

3.3.1. Benefit

Efgartigimod has been shown to effectively reduce IgG antibody levels in clinical trials in healthy subjects and in patients with gMG and ITP.

In both Phase 2 clinical trials, treatment with efgartigimod IV induced a specific, rapid, and profound PD effect and was associated with improvement in clinical signs and symptoms in patients with primary ITP and gMG, separately. In addition, Phase 3 studies with efgartigimod IV in patients with gMG showed that the trial's primary endpoint was met with statistical significance. The primary endpoint was defined as the "percentage of anti-acetylcholine receptor antibody (AChR-Ab) seropositive patients who, during the first cycle, have a reduction of ≥2 points in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score compared to study entry baseline for ≥4 consecutive weeks, with the first reduction occurring no later than 1 week after the last investigational medicinal product (IMP) infusion." A total of 67.7% of AChR-Ab positive patients treated with efgartigimod achieved the primary endpoint compared with 29.7% on placebo ($p<0.0001$). In the overall patient population (AChR-Ab seropositive and seronegative patients), 67.9% of the patients treated with efgartigimod were MG-ADL responders compared with 37.3% on placebo ($p<0.0001$). Other key secondary endpoints for this study were also met with high statistically significance.[13]

Efgartigimod is under development for both the IV and SC administration route. For this Phase 2 CIDP trial, SC administration is planned with a newly developed co-formulation of efgartigimod with rHuPH20 (efgartigimod PH20 SC). The co-formulated material will allow a manual SC injection within a few minutes of greater volumes than without rHuPH20.

Due to the unmet medical need in CIDP for an efficacious treatment with a favorable safety and tolerability profile and more convenient administration for CIDP patients, a SC treatment option for efgartigimod could offer clinically significant benefits to CIDP patients.

There are several lines of evidence to support the conclusion that CIDP is an autoimmune disease mediated by humoral and/or cellular immunity against yet undefined Schwann cell/myelin antigens (see Section 3.1).[8]

The autoimmune etiology is supported further by the efficacy of treatments that target the immune system, including IVIgs, plasma exchange, and corticosteroids, and by evidence of an inflammatory response in the blood and peripheral nerves. Importantly, depletion of serum IgGs from CIDP patients showed promising efficacy in small scale trials.[10]

3.3.2. Risks

To date, no major safety findings have arisen in any of the ongoing and completed trials with efgartigimod (either with the IV or PH20 SC dosing formulations), nor has any pattern of adverse events (AEs) been detected that would raise concerns or alter the potential benefit-risk profile of efgartigimod. The table below lists the potential risks that may be encountered in the trial and the associated strategies to mitigate these risks.

Potential Risks and Mitigation Strategies in Patients With CIDP

Potential clinically significant risk	**Summary of data/rationale for risk**	**Mitigation strategy**
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk of infection.	Exclusion criteria in the current trial (ARGX-113-1802): • Patients with clinically significant active or chronic uncontrolled bacterial, viral, or fungal infections are excluded (exclusion criterion #7). • Patients with total IgG serum levels <6 g/L are excluded (exclusion criterion #8). Infections are considered AESIs and will be monitored, recorded, and reported as described in Section 9.6.2. If a clinically significant infection occurs, IMP administration may be interrupted (Section 8.1). An independent DSMB reviews unblinded data from the current trial (ARGX-113-1802) and from the open-label extension trial (ARGX-113-19802), and will recommend discontinuation or adaptation of the trial if any safety concern is identified (Section 11.1.5).
Injection 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.	Patients will be assessed for injection site reactions at every treatment period visit (Section 1.3 and Section 9.5.1. IMP administration will be performed by trained/authorized site staff or by a trained and authorized home nurse. IMP self-administration or administration by a caregiver is not permitted in the current trial (ARGX-113-1802) and will only be permitted in the open-label extension trial (ARGX-113-1902) after they have completed training and are deemed competent enough to do so by site staff.

AESI=adverse event of special interest; DSMB=data safety monitoring board; IgG=immunoglobulin G; IMP=investigational medicinal product (efgartigimod PH20 SC); rHuPH20=recombinant human hyaluronidase PH20

Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women.

In summary, efgartigimod has been well-tolerated in clinical trials conducted to date.

Please refer to the current Investigator's Brochure (IB), for a full safety and efficacy summary.[9]

An independent Data Safety Monitoring Board (DSMB) will be responsible for ongoing safety monitoring during the trial and will meet on a regular basis (see Section 10.7).

Considering the efficacy and safety data collected to date and the design of the trial that has appropriate measures ensuring safe trial participation, which minimizes the risk to patients participating in this trial, the potential risks identified in association with efgartigimod are justified by the potential benefits gained by patients receiving efgartigimod PH20 SC.

4. OBJECTIVES

Trial objectives are presented by trial stage.

4.1. Stage A: Open-Label Efgartigimod PH20 SC (4–12 Weeks, With Optional 1 Additional Week)

4.1.1. Primary Objective

The primary objective of Stage A is to assess the activity of efgartigimod PH20 SC based on the percentage of patients classified as treatment responders.

4.1.2. Secondary Objectives

Secondary objectives of Stage A are the following:

- To assess the time to clinical improvement
- To determine the treatment effect of efgartigimod PH20 SC based on clinical functional assessments of motor function and muscle strength
- To assess the short-term safety and tolerability of efgartigimod PH20 SC
- To assess the PK of efgartigimod PH20 SC
- To assess the PD effect of efgartigimod PH20 SC
- To assess the immunogenicity of efgartigimod and rHuPH20
- To assess the EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire (EQ-5D-5L)

4.1.3. Exploratory Objectives

[redacted]

4.2. Stage B: Double-Blind, Randomized-Withdrawal of Efgartigimod PH20 SC or Placebo (up to 48 Weeks)

4.2.1. Primary Objective

The primary objective of Stage B is to determine the efficacy of efgartigimod PH20 SC compared to placebo based on the time needed for the occurrence of the first evidence of clinical deterioration.

4.2.2. Secondary Objectives

Secondary objectives of Stage B are as follows:

- To determine the efficacy of efgartigimod PH20 SC compared to placebo based on clinical functional assessments of disease disability and motor function and muscle strength
- To assess the safety and tolerability of efgartigimod PH20 SC
- To assess the PK of efgartigimod PH20 SC
- To assess the PD effect of efgartigimod PH20 SC
- To assess the immunogenicity of efgartigimod and rHuPH20
- To assess the EQ-5D-5L

4.2.3. Exploratory Objectives

[redacted]

5. TRIAL DESIGN

5.1. Overall Design

This is a Phase 2, prospective, multicenter trial to investigate the efficacy, safety, tolerability, PK, and PD of efgartigimod PH20 SC in patients aged 18 years and older with CIDP. This trial will be conducted in 2 stages: An open-label Stage A and a randomized-withdrawal Stage B. After a screening period for all patients and a run-in period for applicable patients (not for treatment-naïve patients; see Section 5.1.2), all patients will enter the open-label Stage A at baseline (D1A) and receive weekly trial treatment (efgartigimod PH20 SC) for up to 12 weeks (with optional 1 additional week). Within this period, upon evidence of clinical improvement (ECI) which is confirmed at 2 consecutive visits, patients will move into the randomized-withdrawal, placebo-controlled Stage B and be randomized at Stage B baseline (D1B) in a 1:1 ratio to efgartigimod PH20 SC or placebo. The randomized-withdrawal Stage B will last up to 48 weeks.

The trial will include the following periods:

- Screening period: up to 28 days (see Section 5.1.1).
- Run-in period: up to 12 weeks (not for treatment-naïve patients; see Section 5.1.2).
- Stage A will be a period of up to 12 weeks (with optional 1 additional week) of open-label treatment of efgartigimod PH20 SC (weekly trial visits) (see Section 5.1.3).
- Stage B will be a period of up to 48 weeks of double-blind, randomized-withdrawal treatment of efgartigimod PH20 SC or of placebo (trial visits once every 4 weeks) (see Section 5.1.4).
- Follow-up: 28 days after the last dose of IMP if the patient does not intend to roll over to the open-label extension (OLE) trial ARGX-113-1902.

Total trial duration for each patient can be up to 80 weeks with a maximum of 61 weeks on IMP.

An independent DSMB will be used in this trial (see Section 11.1.5).

During the different trial periods (run-in, Stage A, and Stage B), there is a permissible window of ±2 days for the trial visits (and ±3 days for the safety follow-up visit) as described in the SoA (see Section 1.3).

The trial schema is provided in Section 1.2.

Patients who discontinue early from treatment, after they have completed the assessments of the current visit will be encouraged to return for all remaining scheduled visits as per SoA (see Section 1.3), unless they withdraw consent (see Section 8).

Trial assessments and procedures are described in Section 9.

5.1.1. Screening

During the screening period of a maximum of 28 days, diagnosis of CIDP will be confirmed by a CIDP confirmation committee (CCC; see Section 11.1.6), and overall eligibility will be confirmed by the medical monitor.

See the SoA in Section 1.3 for the trial procedures that will be performed at screening. Note that additional assessments may be asked for to support the confirmation of CIDP diagnosis (see Section 11.1.6).

If needed, the medical monitor assigned by the sponsor can authorize the extension of the screening period, if this would not impact the analysis of the primary endpoint.

5.1.1.1. Informed Consent

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

Prior to giving informed consent, patients will be instructed not to participate in any other clinical trial that involves a medical intervention or collection of data until the completion of the current trial.

5.1.1.2. Eligibility

Once the patient has provided informed consent prior to any protocol-required assessments that are not part of this patient's routine care, a unique patient identification number will be assigned. Should the patient be withdrawn from the trial, his/her identification number will not be reallocated.

Patients will be classified as eligible if all of the inclusion criteria (see Section 6.1) and none of the exclusion criteria (see Section 6.2) are fulfilled, and eligibility CIDP diagnosis has been confirmed by a CCC (see Section 11.1.6) and by the medical monitor.

If the patient is not eligible, then he/she should be recorded as a screen failure and the reason for screening failure should be documented in the electronic case report form (eCRF).

5.1.1.3. Screen Failures, Re-screening, and Re-testing

A patient who does not meet the eligibility criteria will be considered a screen failure and recorded as such.

A re-test in case of an out-of-range clinical laboratory test value to determine a patient's eligibility is allowed at the discretion of the investigator and in agreement with the sponsor.

A patient may be re-screened once (ie, repeat the full assessments as per general SoA, see Section 1.3.1), only if the patient has not started treatment in Stage A and with the sponsor's written approval.

Examples of conditions under which re-screening may be considered include the following:

- Patients who required treatment for an acute illness (eg, a urinary tract infection) or have a chronic medical problem (eg, uncontrolled hypertension) may be re-screened once the illness has resolved or the medical problem has stabilized.
- The patient has a clinical laboratory test result meeting 1 or more exclusion criteria, which are not consistent with the medical history and clinical evaluation of the patient.
- The patient might not have fulfilled the criteria for evidence of clinically meaningful deterioration (ECMD; see Section 2.2) during the run-in period, but after classification as run-in failure, has fulfilled the criteria of a treatment-naïve patient (ie, not treated with monthly or daily corticosteroids, IVIg or SCIg for at least 6 months) with evidence of

disease activity (ie, documented evidence for worsening on the total adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score, further referred to as "adjusted INCAT score," within 3 months prior to screening compared to previous adjusted INCAT score within 6 months prior to screening).

5.1.2. Run-in Period

After a screening period of maximum 28 days and depending on the type of permitted previous treatments for CIDP, eligible patients will start a run-in period, which will last up to 12 weeks. The following will be done, depending on the prior or current treatment of the patient at screening:

1. Patients, who are treatment-naïve for treatments for CIDP are allowed to skip the run-in period, if there is documented evidence for worsening on the adjusted INCAT score within 3 months prior to screening compared to previous adjusted INCAT score within 6 months prior to screening;

   ***Note**: Patients not treated with pulsed monthly or daily corticosteroids, IVIg or SCIg for at least 6 months prior to screening are considered as equal to treatment-naïve patients.*

2. Patients, who are treated with IVIg or SCIg during screening will stop treatment with IVIg or SCIg at the start of the run-in period (ie, RI-V1);
3. Patients, who are treated with pulsed corticosteroids (IV or oral) or daily oral corticosteroid treatment ≤10 mg during screening will stop treatment with corticosteroids at the start of the run-in period (ie, RI-V1).

Patients are monitored by collecting the grip strength, Inflammatory-Rasch-built Overall Disability Scale (I-RODS) score, Medical Research Council (MRC) sum scoring, adjusted INCAT score, and the Timed Up and Go (TUG) test data. Regular scheduled visits at the trial site are planned every 4 weeks.

Patients will receive appropriate training and instructions to assess every week the disability status by means of I-RODS and grip strength. The patient's I-RODS score and the mean grip strength will be captured, calculated, and transferred to the eCRF. If the patient observes any of the following signals of deterioration, a trial visit should be arranged within 5 working days for an assessment by a physician:

- an I-RODS deterioration by ≥4 points (using the centile metric), and/or
- a mean grip strength deterioration by ≥8 kPa in 1 hand using the handheld vigorimeter.

  ***Note:** Patients will be performing 3 assessments for each hand in arbitrary order (with approximately 30 seconds rest between each assessment) always at approximately the same time during the day. The mean grip strength for each hand will be used to determine disease activity.*

At the trial site, the evaluating physician will then assess if deterioration can be confirmed by fulfilling the criteria for ECMD; see Section 2.2 for definition.

Any patient showing ECMD at the trial site will enter Stage A immediately. If the patient is not providing evidence of ECMD by the end of the run-in period, then he/she should be recorded as a run-in failure.

See the SoA in Section 1.3.1 for other specific trial procedures that will be performed at each visit of the run-in period.

5.1.3. Stage A

All patients with ECMD will start Stage A with the first administration of open-label IMP at Stage A baseline (D1A). After completing all pretreatment baseline assessments, these patients will receive weekly SC administrations of IMP, consisting of efgartigimod PH20 SC, for up to 12 weeks (with optional 1 additional week), with a minimum of 4 SC injections of IMP.

The procedures that will need to be completed at D1A and at the other trial visits are provided in the SoA in Section 1.3.1.

If no safety concerns exist in the opinion of the investigator, patients will be discharged from the center after all planned procedures for that visit according to the SoA have been performed.

Each patient will remain in Stage A and return weekly to the trial site as described in the SoA in Section 1.3.1 until ECI relative to D1A has been identified by the evaluating investigator at 2 consecutive visits (see Section 2.2 for a definition of ECI).

An interim analysis of results will be performed after the first 30 patients in Stage A have reached the end of Stage A (EOSA), see Section 10.6. During the interim analysis, the trial will continue without any interruption, neither for trial enrollment nor for visits or treatments of patients participating in any trial period.

Patients who have not shown ECI at 2 consecutive visits during Stage A will be classified as non-responders. Non-responders will end the trial, will attend a follow-up visit after 28 days after the last administration of IMP, and will be treated by the investigator as considered appropriate.

All patients with confirmed ECI will be randomized to 1 of the 2 treatment arms (SC administration of efgartigimod PH20 SC or placebo) and will start Stage B. Randomization should be performed on the same day as the confirmation of ECI. Therefore, patients with confirmed ECI will have a combination of the EOSA visit and the Stage B baseline (D1B) visit.

Patients who show ECI only at normally the last visit of Stage A (ie, 1 week after A-V12) will be allowed to extend Stage A for a further week with 1 additional consecutive visit. This visit, at which ECI is observed for the first time, will be called the A-V13 visit and will be followed by a consecutive visit 1 week later. The reason for this possible extension of Stage A with 1 week is to get ECI confirmed at a consecutive visit 1 week later (and, if ECI is confirmed, to randomize the patient [ie, the patient will start Stage B]). In case ECI is not confirmed after an additional week of Stage A, an EOSA visit will be performed and the patient will end the trial (after a follow-up visit 28 days following the last IMP administration). See also Section 7.1.2 for detailed information of IMP administration in Stage A.

During Stage A, IMP will be administered at the site after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses and after all assessments needed for determination of ECI.

During Stage A, all patients will receive training for self-administration of IMP (foreseen in the OLE trial, not in the ARGX-113-1802 trial) as specified in the SoA in Section 1.3.

5.1.4. Stage B

Evaluations at screening, during the run-in period (visit RI-V1 to visit RI-V4), and confirmation at Stage A baseline (D1A; visit A-V1) before first treatment in Stage A and the treatment response during Stage A will be used to determine each patient's eligibility for randomization in Stage B at Stage B baseline (D1B).

Patients with ECI during Stage A will be randomized at Stage B baseline (D1B) in a 1:1 ratio to receive weekly SC administrations of efgartigimod PH20 SC or placebo.

All patients randomized to the double-blind, randomized-withdrawal Stage B will be dosed with IMP weekly but will return to the clinic at 4-week intervals (once every 4 weeks). At each of these visits, specific procedures, as specified in the SoA in Section 1.3.2, will be performed.

Patients will be discharged from the trial center after all planned procedures for that visit according to the SoA in Section 1.3.2 have been performed and if no safety concerns exist in the opinion of the investigator.

For the purpose to lessen the burden on patients as much as possible, the following solutions for in-between site visit IMP SC administrations will be proposed: Administration by a home nurse or concierge service for visit at the trial site. Upon agreement with the investigator, site personnel, and the patient, the most suitable solution will be provided for IMP administration in between trial visits. Administration of IMP will occur always within a time window of ±2 days with respect to the pre-planned date of administration. Patients will receive a treatment schedule plan to ensure that timing of IMP administration will be observed. The patient will be asked to return used and unused medication at the next visit, during which IMP accountability will be performed. On the scheduled trial visits, IMP will be administered at the site after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses and after all assessments needed for determination of clinical deterioration.

When 88 events have been observed for the primary endpoint analysis of Stage B (see sample size determination for Stage B in Section 10.3), then the trial will stop. In that case, patients in Stage A and Stage B will perform an early discontinuation visit and patients who are receiving IMP will be given the opportunity to continue efgartigimod PH20 SC treatment in the OLE trial (in this case the early discontinuation visit of the ARGX-113-1802 trial can coincide with the roll over visit). Additionally, at the time of the 88th event, patients in run-in will also be given the option to roll over to the OLE trial after performing an early discontinuation visit. Patients who will not roll over to the OLE trial, will attend a follow-up visit 28 (±3) days after the last IMP dose.

Patients will be given the opportunity to continue efgartigimod PH20 SC treatment in an OLE trial ARGX-113-1902 if any of the following 3 conditions occur:

1. The patient experiences clinical deterioration (ie, worsening in adjusted INCAT score) during Stage B.

   ***Note**: Clinical deterioration needs to be confirmed by an unscheduled visit that is to be planned 3-7 days after the first adjusted INCAT score increase of 1 point (or at a following trial visit if planned at that time). For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required. In case the patient experiences clinical deterioration, the visit will become an early discontinuation visit of ARGX-113-1802 and the patient can roll over to the*

ARGX-113-1902 trial (in this case the early discontinuation visit will be combined with the first visit of the ARGX-113-1902 trial).

2. The patient completes week 48 visit of Stage B without any clinical deterioration (see Section 2.2).
3. Recording of the 88th event during Stage B and the patient is receiving IMP in either Stage A or Stage B. An event is a worsening of the adjusted INCAT score in any of patients treated during Stage B (see Section 2.2 and Section 10.3).

Additionally, at the time of the 88th event, patients in run-in will also be given the option to roll over to the OLE trial after performing an early discontinuation visit.

The OLE will be a separate trial ARGX-113-1902 with details described in its own protocol.

During Stage B, patient will receive further training for self-administration of IMP (foreseen in the OLE trial, not in the ARGX-113-1802 trial) as specified in the SoA in Section 1.3.2.

Patients who have clinical deterioration or who complete the week 48 visit also have the possibility to enter the safety follow-up period and complete the trial without rolling over to the OLE trial. These patients will be treated as considered appropriate by the investigator.

5.1.5. Unscheduled Visit

It is at the investigator's discretion, or on request of the patient, to initiate an unscheduled visit, if deemed necessary for the patient's safety and well-being.

An unscheduled visit is to be planned for: 1) safety reasons, 2) assessment of ECMD during the run-in period, 3) assessment of efficacy during Stage B (eg, confirmation of worsening on the adjusted INCAT score of 1 point), or 4) any other reason.

All such visits will be documented in the eCRF with any additional required documentation based on the nature of unscheduled visit.

Procedures that can be performed at an unscheduled visit are defined in the SoA in Section 1.3. The investigator can decide which of the assessments need to be performed at each unscheduled visit. If, for example, the unscheduled visit is used to confirm ECMD during run-in (which needs to be observed at the trial site) or clinical deterioration during Stage B, the assessments as listed for the scheduled visits in the corresponding period will need to be performed (see the SoA in Section 1.3).

The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary, then additional diagnostic tests may be performed based on investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit page of the eCRF.

5.1.6. Follow-up

A follow-up visit will be planned 28 days after the last dose of IMP (in case of early discontinuation from IMP or the trial), or in case a patient does not meet the criteria for ECI in Stage A [non-responder]) or 28 days after the last dose in Stage B if the patient does not intend to roll over to the OLE trial ARGX-113-1902.

Procedures performed at the follow-up visit are defined in the SoA in Section 1.3.

5.2. Scientific Rationale for Trial Design

The trial design uses some key elements from the PATH trial (van Schaik et al, 2018).[15]
A treatment period (Stage A) is foreseen for all patients who showed evidence of disease activity during the run-in period.

The run-in period has 2 purposes:

- Selecting for patients with evidence of clinical disease activity (enrichment design);
- Ensure that both, the half-life of the previous drug (if applicable) had elapsed and the clinical effect would not jeopardize the efficacy analysis of the current trial.

The pre-randomization observation period on treatment (Stage A) can be of any length between 4 and 13 weeks. The post-withdrawal observation period (ie, for patients in the placebo group during Stage B) in this trial has a maximum duration of 48 weeks, but applies during this period the time to event approach (early escape design). As with the early escape design, careful attention has been paid to procedures for monitoring patients and assessing trial endpoints to ensure that patients failing on an assigned treatment are rapidly identified.

The advantages of this trial design are that individuals receiving the experimental intervention continue to do so only if they respond, whereas individuals receiving placebo do so only until their symptoms return.

Additional advantage of this design is to study the long-term efficacy or safety (withdrawal effect). A disadvantage is the longer overall trial period, which has been extended from typical 24 weeks to 48 weeks.

This trial design allows to collect information on the onset of therapeutic effect as well as information if the effect continues after withdrawal from medication or if there is a rebound phenomenon (placebo group). Furthermore, this trial will also generate data of the placebo response in such a population that is of interest for further clinical development.

Any difference that emerges between the group receiving continued treatment and the group randomized to placebo in Stage B will demonstrate the effect of the active treatment.

All eligible patients will start the participation in this trial through an open-label period (Stage A), in which they will all receive active treatment. Such a choice was perceived necessary for the purpose to offer to all patients with active disease a minimal treatment with efgartigimod PH20 SC, even for those patients who would be randomized to the placebo arm after this period (in Stage B). Stage A has a variable duration at minimum 4 weeks up to 12 weeks (with optional 1 additional week), during which the patient will be treated with weekly SC administrations until clinical improvement has been achieved and maintained in 2 concurrent visits. This variable duration has been chosen to achieve the maximal IgG reduction, which will maximize the duration of effect. A maximum number of injections is set at 12 (or 13 in case of an optional additional week), in line with clinical practice for other therapies (3 months).

As introduction into the placebo arm, an initial open-label treatment with efgartigimod PH20 SC (Stage A) is foreseen for all patients. This allows patients to receive active treatment before potential randomization to placebo (during Stage B), which would make the design more

acceptable within the current context of highly effective treatment standards in this debilitating disease. In addition, Stage A followed by randomization to the placebo arm allows to establish how long the treatment effect will last before clinical evidence of disease activity will appear again. In this way, the trial allows to evaluate through [redacted], if a personalized treatment schedule might be an option in clinical practice. Indeed, the [redacted] might help to identify signs of disease activity before clinical symptoms emerge. It can also not be excluded that a number of durable long-lasting remissions after open-label Stage A may occur. Hereby the placebo arm may confirm such a finding.

Patients with clinical deterioration, as measured by an increase of the adjusted INCAT score at any time during Stage B, will be offered the opportunity to roll over to a separate OLE trial with weekly dosing of efgartigimod PH20 SC. Double blinding of the original treatment assignment will be maintained throughout the trial, even at the time of withdrawal.

The possibility to roll over to the OLE trial would make the trial attractive for patients who took an advantage from open-label treatment during Stage A and know that the effective open-label treatment will be available for them again (in the OLE trial) despite of the option to be randomized to placebo and to potentially deteriorate in the randomized Stage B of the trial.

All efficacy, safety, and quality-of-life assessments used in this trial are standard, ie, widely used (including in CIDP trials) and recognized as reliable, accurate, and relevant.[15,16]

[redacted] The total human IgG levels themselves are only a measure on how long the decrease of IgG levels is ongoing after suspension of treatment with efgartigimod PH20 SC. This will become a relevant reference marker for those patients, who after the induction period are randomized to the placebo arm. It will help to evaluate if there is a specific delay between the return of IgG levels and the occurrence of either clinical symptoms or signs, or other parameters such as inflammatory or [redacted].

5.3. Justification for Dose

A dose of 1000 mg efgartigimod PH20 SC was selected for both Stage A and Stage B. Based on population PK/PD modeling, this dose of efgartigimod PH20 SC (weekly administration) is predicted to be comparable to 10 mg/kg efgartigimod weekly administered as IV infusion with respect to effect on IgG levels. The efgartigimod 10 mg/kg IV dose:

1. Resulted in transient clinical efficacy in a Phase 2 trial in ITP patients and a prolonged clinical effect in a Phase 2 trial in MG patients following 4 weekly infusions.
2. Was shown to result in close to saturated PD effect:

Dosing higher or more frequently than weekly is not expected to result in an improved PD effect (ie, further lowering of autoantibodies) and/or clinical effect and may be associated with a less optimal risk/benefit ratio. Dosing lower is expected to result in a lower PD effect and thus is likely to result in a less consistent and/or incomplete clinical response, which is undesirable given the serious and chronic manifestations of CIDP. Therefore, weekly dosing is favorable until patients are in a stable clinical condition.

3. Demonstrated a favorable safety profile in Phase 2 trials in MG and ITP patients.

In addition, based on favorable phase 3 results in patients with MG, efgartigimod IV at a dose of10 mg/kg has been approved in the United States (US) and in the EU (in both regions for AChR-Ab seropositive patients) and in Japan (for patients who do not have sufficient response to steroids or nonsteroidal immunosuppressive therapies).

A study in healthy participants demonstrated that after 4 weekly injections of efgartigimod PH20 SC 1000 mg, the pattern of total IgG level reduction over time was comparable to that observed after 4 weekly infusions of efgartigimod IV 10 mg/kg.

rHuPH20, as Hylenex, has been approved in the US. Coformulations of rHuPH20 with other active ingredients have been approved in the US and the EU (eg, HERCEPTIN HYLECTA/Herceptin SC, RITUXAN HYCELA/MabThera SC, HYQVIA/HyQvia, respectively), with a rHuPH20 concentration of 2000 U/mL for a SC injection volume in the range of 5 to 13.4 mL.

5.4. Measures to Minimize Bias: Randomization and Blinding

Stage A will be open-label with administration of efgartigimod PH20 SC.

In Stage B, patients will be randomized to double-blind SC efgartigimod PH20 SC or placebo in a 1:1 ratio. Patients will be stratified according to their prior CIDP medication and the decrease of adjusted INCAT score during Stage A by the following:

- Prior CIDP medication:
  - Treatment-naïve (see inclusion criterion #6 in Section 6.1 for definition);
  - Pulsed corticosteroid treatment or oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day;
  - IVIg or SCIg treatment.
- Adjusted INCAT score:
  - No change in adjusted INCAT score during Stage A;
  - Adjusted INCAT score decrease of ≥1 point during Stage A.

Except for unblinding for safety reasons, Stage B will be double-blind to treatment assignment during the entire randomized-withdrawal period, even if the patient withdraws from the trial or enters the OLE trial ARGX-113-1902. The treatment that each patient receives will not be disclosed to the investigator, investigational site staff, patient, sponsor, or the sponsor's designated contract research organization (CRO). The trial will be unblinded following the final database lock.

Refer to Section 7.2 for the preparation and administration of the IMP, thereby keeping the blind during Stage B.

The sponsor will appoint a DSMB consisting of an independent group of clinical experts, who will not participate in the trial as active investigators. The DSMB will be supplemented by an independent statistician. The objective of the DSMB will be to review all unblinded safety data and determine if there is an imbalance in treatment arms assignment regarding safety events. The DSMB will advise the sponsor on the continuation, modification, or termination of the trial.

More detail on the DSMB is provided in Section 11.1.5.

5.4.1. Two Physician Concept

In addition to the double blinding of IMP in Stage B of the trial, the two physician concept will be used to achieve blinding for the evaluation of clinical endpoints, in which there will be 2 physician roles: a treating physician and an evaluating physician.

For each role, preferably 1 deputy will be nominated at each center. Therefore, in total at least 4 staff members should be involved in the treatment and evaluation of patients at each center.

Throughout this protocol, references to the “treating physician” and “evaluating physician” include their respective deputies.

The (principal) investigator who is responsible for the conduct of the trial and for supervision of the management of individual patients at the center should not take the role of the evaluating physician.

5.4.1.1. Treating Physician

The treating physician will be responsible for all aspects of treatment and clinical management of the patient, including the management of clinical symptoms. He/she will have the same level of blinding as the patient.

The treating physician will perform the following activities:

- Physical examinations
- Assessment of vital signs
- Evaluation of the patient’s subjective findings (eg, how the patient feels and if there were any symptoms suggesting an AE)
- Assigning (through interactive response technology [IRT] randomization) and monitoring the administration of the trial medication
- Evaluating and managing (serious) AEs, concomitant medication and laboratory results
- Loading patient’s data into the electronic system, including the results from ECI and/or ECMD related assessments
- Undertaking relevant steps in response to ECI or ECMD evidence (which will be provided by the evaluating physician)

The treating physician cannot be involved in evaluating adjusted INCAT and I-RODS scores or assessment of mean grip strength, MRC, and TUG test. However, the treating physician will have access to results of ECI and ECMD assessments.

5.4.1.2. Evaluating Physician

The evaluating physician will oversee the scoring of:

- adjusted INCAT and I-RODS, and
- and all the standardized neurological examinations needed, including the assessment of:
  - mean grip strength
  - MRC
  - TUG test

The evaluating physician will make an assessment of clinical deterioration.

He/she will also oversee the evaluation of the following PRO tools:

- EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire (EQ-5D-5L)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

See Section 9 for a description of the different assessments.

Throughout the whole duration of the trial, the evaluating physician will not seek nor collect any treatment-related information (eg, AEs, treatment compliance, interruption or discontinuation, etc.) from the patient or from the treating physician.

The interaction with the patient will be restricted to the neurological evaluation. The evaluating physician will not be allowed to talk with the patient about AEs, or any other issue that could potentially disclose the patient's treatment.

Thus, the Evaluating Physician will be completely blinded to all aspects related to the patient's treatment, including the assessment of side effects and drug administration problems.

5.4.2. Emergency Unblinding Procedure

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

Unblinding by the investigator should occur only in the event of an AE for which it is necessary to know the randomized treatment to determine an appropriate course of therapy for the patient.

If possible, the investigator should first discuss options immediately with the medical monitor and sponsor, with due consideration of the safety of the patient. If the investigator must identify the treatment assignment of an individual patient, the principal investigator/treating physician is to contact the IRT.

If the blind is broken, it may be broken only for the patient concerned, and the IMP treatment assignment should not be revealed to the trial team members from the sponsor, nor from the sponsor's designated CRO, or pharmacy personnel.

Patients for whom the code has been broken by the investigator will be withdrawn from the trial and all efforts should be made to conduct the early discontinuation visit as well as the follow-up visit 28 days after the last IMP dose (see Section 8.3). All efficacy data up until the code break will be included in the modified intent-to-treat (mITT) and per protocol (PP; in case of no major protocol deviations until the code break) analysis sets.

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

5.5. End of Trial Definition

The end of trial is defined as the last patient last visit in the ARGX-113-1802 trial, ie, any of the following:

- the last visit before roll over to the OLE trial, or
- the follow-up visit 28 days after the last IMP dose for patients not participating in the OLE trial.

See Section 11.1.10 for trial and site start and closure.

5.6. Roll Over to Open-label Extension (OLE) Trial

Patients who are receiving IMP, and in the opinion of the investigator benefit from trial treatment at week 48 or who, while on treatment, experienced clinical deterioration during Stage B (ie, worsening in adjusted INCAT score; see Section 5.1.4) will be offered the option to roll over to a long-term, single-arm, OLE trial, during which they will be treated weekly with SC efgartigimod PH20 SC. The dose and frequency used in the OLE is the same as is given to patients enrolled to Stage A of this trial.

Patients who are receiving IMP in Stage A or Stage B, or are in run-in at the moment of recording of the 88th event in the trial, will perform an early discontinuation visit and will be offered the option to roll over to the OLE trial, as the ARGX-113-1802 will stop at this moment. An event is a worsening of the adjusted INCAT score (see Section 2.2 and Section 10.3) in any of patients treated during Stage B.

Patients who discontinue early from randomized treatment for pregnancy reasons or for an (S)AE that might jeopardize the safety of the patient will not be offered the option to roll over to the OLE trial.

It will be documented if a patient will roll over to the OLE trial.

5.7. Protocol Deviations

The investigator should not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority as per local regulation, except where necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (eg, change of telephone numbers, …). The investigator (or designee) should document and explain any deviation from the approved protocol.

Protocol exemptions or waivers will not be approved by the sponsor.

6. TRIAL POPULATION

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

6.1. Inclusion Criteria

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

1. Ability to understand the requirements of the trial, provide written informed consent (including consent for the use and disclosure of research-related health information), willingness and ability to comply with the trial protocol procedures (including required trial visits).
2. Male or female patient aged 18 years or older, at the time of signing the informed consent.
3. Diagnosed with probable or definite CIDP according to criteria of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS, 2010),[2] progressing or relapsing forms.
4. CIDP Disease Activity Status (CDAS)[3] score ≥2 at screening (see Section 11.6).
5. An INCAT score ≥2 at the first run-in visit (RI-V1; for patients entering run-in) or Stage A baseline (A-V1; for treatment-naïve patients with documented evidence for worsening on the total adjusted INCAT disability score within 3 months prior to screening). Patients with an INCAT score of 2 at trial entry must have this score exclusively from the leg disability score; for patients with an INCAT score of ≥3 at trial entry, there are no specific requirements for arm or leg scores.
6. Fulfilling any of the following treatment conditions:
   - Currently (ie, within the last 6 months) treated with pulsed corticosteroids, oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg, and the patient is willing to discontinue this treatment at the first run-in visit (RI-V1); OR
   - Without previous treatment (treatment-naïve); OR
   - Treatment with corticosteroids and/or IVIg or SCIg discontinued at least 6 months prior to screening.

   ***Note**: Patients not treated with monthly or daily corticosteroids, IVIg or SCIg for at least 6 months prior to screening are considered as equal to treatment-naïve patients.*
7. Women of childbearing potential who have a negative pregnancy test at screening and a negative urine pregnancy test up to Stage A baseline (D1A).

8.a. Women of childbearing potential must use an acceptable method of contraception from signing the ICF until the date of the last dose of IMP (see Section 11.3).

9. Inclusion criterion removed in protocol amendment 4.

6.2. Exclusion Criteria

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

1. Pure sensory atypical CIDP (EFNS/PNS definition[2]).
2. Polyneuropathy of other causes, including the following:
   - Multifocal motor neuropathy
   - Monoclonal gammopathy of uncertain significance with anti-myelin-associated glycoprotein immunoglobulin M (IgM) antibodies
   - Hereditary demyelinating neuropathy
   - Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin change syndromes
   - Lumbosacral radiculoplexus neuropathy
   - Polyneuropathy most likely due to diabetes mellitus
   - Polyneuropathy most likely due to systemic illnesses
   - Drug- or toxin-induced polyneuropathy
3. Any other disease that could better explain the patient's signs and symptoms.
4. Any history of myelopathy or evidence of central demyelination.
5. Current or past history (within 12 months of screening) of alcohol, drug or medication abuse.
6. 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 patient or could affect adherence with the trial protocol.

   ***Note*:** *At screening, suicidality will be assessed using the Columbia-suicide severity rating scale (C-SSRS) (see Section 9.2); patients with a high suicide risk will be excluded from the trial (ie, patients 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 above 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.*
7. Patients with clinically significant active or chronic uncontrolled bacterial, viral, or fungal infection at screening, including patients who test positive for an active viral infection at screening with (see Section 9.1 for more information):
   - Active Hepatitis B Virus (HBV): serologic panel test results indicative of an active (acute or chronic) infection;
   - Active Hepatitis C Virus (HCV): serology positive for HCV-Ab;
   - Human Immunodeficiency Virus (HIV) positive serology associated with an Acquired Immune Deficiency Syndrome (AIDS)-defining condition or with a cluster of differentiation 4 (CD4) count $\leq$200 cells/mm^3.
8. Total IgG level <6 g/L at screening.

9.a. Treatment with the following:

- **Within 3 months (or 5 half-lives of the drug, whichever is longer) before screening**: plasma exchange or immunoadsorption, any concomitant Fc-containing therapeutic agents or other biological, or any other investigational product;
- **Within 6 months before screening**: rituximab, alemtuzumab, any other monoclonal antibody, cyclophosphamide, interferon, tumor necrosis factor–alpha inhibitors, fingolimod, methotrexate, azathioprine, mycophenolate, any other immunomodulating or immunosuppressive medications, and oral daily corticosteroids >10 mg/day.

  Note: *Patients using IVIg, SCIg, pulsed corticosteroids, and oral daily corticosteroids ≤10 mg/day can be included.*
- Patients who (intend to) use prohibited medications and therapies (see Section 7.4.2) during the trial.

10.a. Pregnant and lactating women and those intending to become pregnant during the trial.

11. Patients with any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of CIDP.

12.a. Patients who received a live-attenuated vaccine fewer than 28 days before screening. Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not exclusionary.

13. Patients who have a history of malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before the first IMP administration. Patients with the following cancer can be included anytime:

    - Adequately treated basal cell or squamous cell skin cancer,
    - Carcinoma in situ of the cervix,
    - Carcinoma in situ of the breast, or
    - Incidental histological finding of Prostate cancer (TNM [tumor, nodes, and metastases classification] stage T1a or T1b).

14. Patients who previously participated in a trial with efgartigimod and have received at least 1 administration of IMP.

15. Patients with known medical history of hypersensitivity to any of the ingredients of IMP.

16. Patients with clinical evidence of other significant serious disease or patients who underwent a recent or have a planned major surgery, or any other reason which could confound the results of the trial or put the patient at undue risk.

6.3. Lifestyle Considerations

There are no specific lifestyle considerations for this trial.

7. TREATMENTS AND THERAPIES DURING THE CONDUCT OF THE TRIAL

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

In open-label Stage A, IMP is efgartigimod PH20 SC. In the double-blind Stage B, IMP is efgartigimod PH20 SC and placebo.

7.1. IMP(s) Administered

Efgartigimod is a modified human IgG1 Fc fragment with increased affinity to human FcRn. rHuPH20 is an enzyme used to increase the dispersion and absorption of co-administered therapeutics when administered SC. Efgartigimod and rHuPH20 are co-formulated and will be administered as a single SC injection.

IMP will be provided by the sponsor and is manufactured in accordance with Good Manufacturing Practice regulations.

The efgartigimod PH20 SC formulation will be provided in a vial at a concentration of 165 mg/mL or 180 mg/mL (new concentration) for efgartigimod and 2000 U/mL for rHuPH20 (also referred to as ARGX-113/rHuPH20). Each dose of efgartigimod PH20 SC will include 1000 mg efgartigimod. Note that there will be a transition period during which both formulations of efgartigimod PH20 SC (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL) will be used. After this transition period, all patients will receive the efgartigimod PH20 SC formulation with efgartigimod at the higher concentration of 180 mg/mL. The formulation with the higher concentration of efgartigimod (180 mg/mL) reduces the dosing volume for each SC injection.

Placebo will be vehicle (with 2000 U/mL of rHuPH20) provided in a vial as ready SC formulation. For both efgartigimod PH20 SC formulations (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL), a corresponding placebo is available containing placebo drug product at the same volume and in the same vial as the active drug product.

Refer to the pharmacy manual for detailed instruction of IMP administration.

The vials will be labeled as required per country requirements.

7.1.1. Run-in Period

No IMP will be administered during the run-in period.

All eligible patients who are **not** considered treatment-naïve (for definition see inclusion criterion #6 in Section 6.1) will participate in the run-in period. Eligible patients, who are treated at time of screening with pulsed corticosteroids, or oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg will stop taking their current treatment for CIDP at the time they start the run-in period (ie, RI-V1).

Eligible treatment-naïve patients, including patients not treated with corticosteroids, IVIg or SCIg for at least 6 months prior to screening, will start immediately with Stage A after the screening period, if during screening documented evidence for worsening on the adjusted INCAT score within 3 months prior to screening is available compared to previous adjusted INCAT score within 6 months prior to screening.

7.1.2. Stage A: Open-label

IMP will be administered to all patients in Stage A as efgartigimod PH20 SC in the abdominal skin area. IMP will be administered weekly until ECI is observed by the investigator for 2 consecutive visits, thereby considered confirmed ECI. Each patient will receive at least 4 and maximum 12 weekly doses of IMP (up to the A-V12 visit). Patients who show ECI only at the last visit in Stage A (ie, 1 week after A-V12) will be allowed to extend Stage A for a further week with 1 additional consecutive visit (A-V13) with an injection at week 12 (ie, a 13th injection). The reason for this possible extension is to get ECI confirmed at a consecutive visit (and, if confirmed, to randomize the patient in Stage B). In case the ECI is not confirmed after an additional week of Stage A, the patient will have an EOSA visit, followed by a safety follow-up visits 28 days after last IMP administration and will end the ARGX-113-1802 trial (see Section 5.1.3).

Below is an overview of the minimum and maximum IMP administrations in Stage A:

Minimum number of IMP administrations in Stage A	4 IMP administrations at: A-V1 (ie, D1A), A-V2, A-V3, and A-V4. In case ECI is observed at A-V4 and also 1 week after A-V4, the patient will be randomized and will start Stage B; ie, in this case, the patient will not have a A-V5 visit, EOSA procedures will be followed and the patient will have a D1B visit (this visit will be a combination of EOSA and D1B).
Normal maximum number of IMP administrations in Stage A	12 IMP administrations at: A-V1 (ie, D1A) through A-V12. In case ECI is observed at A-V12 and also 1 week after A-V12 (ie, ECI is confirmed), the patient will be randomized and will start Stage B; ie, in this case, the patient will have a combination of the EOSA visit and the D1B visit 1 week after A-V12. In case no ECI is observed at A-V12 and also not 1 week after A-V12, this visit 1 week after A-V12 will then be the EOSA visit (and the patient will end the trial after performing a safety follow-up visit 28 days after the last IMP administration).
Optional 1 additional week of IMP administration	In case no ECI is observed at A-V12, but the patient has ECI 1 week after A-V12, this visit 1 week after A-V12 will then become an additional visit called A-V13 at which the patient will receive another IMP administration (resulting in a total of 13 IMP administrations). The patient will then need to come back 1 week after the A-V13 visit for the EOSA visit to confirm ECI. If the

	patient has ECI at this visit (ie, ECI is confirmed), the patient will be randomized and will start Stage B (ie, the patient will have a combination of the EOSA visit and the D1B visit 1 week after the A-V13 visit). If the patient does not have ECI at the EOSA visit 1 week after the A-V13 visit, the patient will end the trial after performing a safety follow-up visit 28 days after the last IMP administration.

7.1.3. Stage B: Double-blind, Randomized-withdrawal

IMP in Stage B will be either efgartigimod PH20 SC or placebo, administered in the abdominal skin area.

During Stage B, all patients will receive IMP weekly up to 48 weeks.

Patients who have clinical deterioration or who complete the week 48 visit will have the possibility to enter the safety follow-up period and complete the ARGX-113-1802 trial or have the possibility to roll over to the OLE trial (see Section 5.1.4).

7.2. Preparation, Handling, Storage, Administration, and Accountability

Refer to the Pharmacy Manual for information about the temperature conditions for IMP transit and storage and the IMP preparation, including the volume of efgartigimod PH20 SC or placebo to be administered.

Efgartigimod PH20 SC will be provided as a sterile, clear to opalescent, yellowish solution for SC injection.

Placebo will be provided as a sterile, colorless, clear solution for injection in glass vials with the same formulation as the efgartigimod PH20 SC solution for injection, but without the active ingredient.

The vials for the double-blind Stage B will be covered with a blinding shell.

The trained and authorized staff will use an amber colored syringe for preparation and administration of IMP. The administration is then performed by the site staff who prepared the syringe.

For each injection, the initiation and completion times (hour and minute) and details of any interruptions or premature discontinuation of injections will be recorded and will be transferred to the eCRF. The start will be marked as the moment of start pressing the plunger and the end will be marked as the completion time of administration of the total volume of IMP.

Only patients enrolled in the trial shall receive IMP and only authorized site staff shall supply IMP, administer IMP, or train the home nurse on IMP administration. Each patient will receive a specific training for self-administration (foreseen in the OLE trial, not in the ARGX-113-1802 trial) and a manual on preparation, handling, storage and administration of the IMP. The mode of administration (at the site during a trial visit, home nurse, or concierge service for visit at the trial site) will be recorded in the eCRF or (in case of administration by a home nurse or concierge service for visit at the trial site) will be documented and transferred to the eCRF.

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).

Further guidance and information for the final disposition of unused IMP are provided in the pharmacy manual.

7.3. IMP Compliance

Patients will receive weekly SC administrations of IMP over a maximal treatment period of 61 weeks (up to 12 weeks with optional 1 additional week in Stage A and 48 weeks in Stage B).

During Stage A, all efforts will be made to ensure that the patient receives at least 4 administrations of IMP within the allowed time windows. In addition, during the rest of the trial, also all efforts will be made to ensure that the patient receives the IMP as planned.

The treating physician should ensure treatment compliance by stating that compliance is necessary for the potential effectiveness of patient's treatment and for the validity of the trial.

The prescribed dose, timing, and mode of administration cannot be changed. All dates and start and end time of IMP administration and any deviations from the intended regimen must be recorded (see Section 7.2).

Any patient who misses a single dose (within the window of ±2 days of the planned administration day) will not make up for the missed dose and will receive the next dose as scheduled in the SoA (see Section 1.3). Also, in case a dose needs to be delayed for more than 5 days, the dosing should be skipped to ensure 2 consecutive doses are given with an interval of at least 3 days.

The patient must not miss more than 2 consecutive doses and must not miss more than 10% of the total planned doses that should have been taken (for example, 1 missed dose in Stage A is allowed and a maximum of 4 missed doses during the 48-week Stage B period will be permitted, if doses missed are not consecutive) (see also Section 9.7).

If a patient misses more than 2 consecutive doses or more than 10% of the total planned doses that should have been taken, the patient will be excluded from the per protocol analysis.

In case of lack of compliance, the number of missed doses will be captured, but the patient can remain in the trial (unless the patient withdraws his/her consent). The investigator should discuss the reason with the patient and should stress the importance of IMP compliance.

7.4. Prior Treatments and Concomitant Medications

Eligible patients, who are treated at the time of screening with pulsed corticosteroids, or oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg will stop taking their current treatment for CIDP at the time they start the run-in period (ie, RI-V1).

Clinically relevant prior treatments received by the patient including:

- Previous treatments or procedures for CIDP with patient's response and reason for changing treatment/dose
- Previous Non-CIDP treatment or procedures in the last 6 months

- Treatment related to malignancies in at least the last 3 years

must be recorded in the eCRFs. Information should include start and stop dates and tick box for those continuing as concomitant medication.

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

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification.

Any vaccine or medication, including over-the-counter and prescription medicines, vitamins, and/or herbal supplements, that the patient is receiving at the time of enrollment or receives during the trial must be recorded with the following information provided:

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

As part of prior medication, details collected at screening should include all information the patient or caregiver can remember about previous vaccinations received, including administration date and brand name, if known (note: if in the past a same vaccine was received more than once, including as booster, only the last one is to be collected). Any vaccination received during the trial, including administration date and brand name, will be entered as concomitant medication.

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

Symptomatic treatments will be left to the discretion of the investigators.

7.4.1. Permitted Medication

Medication not used for the treatment of CIDP is permitted, if not part of the groups of medication specifically prohibited in Section 7.4.2.

Any kind of vaccination, except for live-attenuated vaccines, is allowed at the discretion of the investigator. In patients who receive a vaccination during the trial, data on the interaction vaccine-IMP and on the efficacy of the vaccine shall be collected.

7.4.1.1. Patient's Medication in Between Trial Visits

As this is an outpatient trial, special care will be taken in questioning the patients on any medication, and patients will be asked to document details of concomitant medications, which will be evaluated by site personnel and transferred by an authorized trial team member to the eCRF. In addition, for IMP administrations in between trial visits, the home nurse will record the IMP dosing information on a source document and will provide this source document to the trial site for entry in the eCRF.

7.4.1.2. Treatment in the Event of Clinical Deterioration During Stage B

If clinical deterioration, defined as an increase of adjusted INCAT score with respect to Stage B baseline (see Section 2.2), is detected in any patient during Stage B, then the patient will be eligible immediately for enrollment in the OLE trial ARGX-113-1902 after completing the early discontinuation visit (which corresponds with the first visit of the OLE trial). Patients will also have the possibility to enter the safety follow-up period and complete the trial without rolling over to the OLE trial. These patients will be treated as considered appropriate by the investigator (see Section 5.1.4).

Double-blinding will be maintained about the original treatment assignment during the whole trial, even at the time of trial completion or withdrawal from the trial.

7.4.2. Prohibited Medications

Medication for treatment of CIDP will be continued during the screening period and will be discontinued from the start of the run-in period (RI-V1) onwards:

- Intravenous or subcutaneous immunoglobulin therapy;
- Pulsed corticosteroids and oral daily corticosteroids ≤10 mg/day.

  ***Note**: If tapering is required, it should be initiated during the screening period according to local practice.*

The following medications or treatments are not permitted from signing the ICF at screening during the entire trial:

- Plasmapheresis;
- Total lymphoid irradiation;
- Any other IgG therapy;
- Any stem cell-based therapy, including bone marrow transplantation like autologous stem cell transplant (ASCT) and allogenic cells transplants;
- Any cytokine or anti-cytokine therapy;
- Systemic corticosteroids, including oral, for any other indication than CIDP;
- Cyclophosphamide, interferon, tumor necrosis factor–alpha inhibitors, fingolimod, methotrexate, azathioprine, mycophenolate, or any other immunomodulating or immunosuppressive medications or procedures;
- Rituximab, alemtuzumab, or any other monoclonal antibody for immunomodulation;
- Any investigational drug or experimental procedure;
- Live-attenuated vaccines

  ***Note**: Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not prohibited.*
- Use of complementary therapies, including traditional Chinese medicines and herbal remedies, containing any of the following: naturally derived glucocorticoids; medication with clinical evidence-based immunosuppressive, immunomodulatory, peripheral or central nervous system effects; or procedures (eg, acupuncture) for any neurological

condition within 4 weeks or 5 half-lives (whichever is longer) prior to IMP dosing and agreed not to use during the trial.

If the administration of a non-permitted concomitant drug becomes necessary during the clinical trial, eg, because of AEs, the patient has to discontinue IMP, as described in Section 8.2.

7.5. Medical Care of Patients after End of Trial

After a patient has completed the trial, but is not eligible or not willing to participate in the OLE trial ARGX-113-1902, or has withdrawn/discontinued early, the most appropriate treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice depending on the patient's individual needs.

7.6. Dose Modification

There will be only 1 dose of IMP for each IMP administration. Dose modification is not allowed during the trial.

7.7. Intervention After the End of the Trial

The OLE trial ARGX-113-1902 will be open to patients if the following criteria are met:

- Clinical deterioration during Stage B (defined as an increase of adjusted INCAT score with respect to Stage B baseline; see Section 2.2);
- Completion of the week 48 visit of Stage B without any clinical deterioration (see Section 2.2);
- The 88th event needed for the primary endpoint analysis is observed (see Section 10.3); in this case all patients who are receiving IMP in either Stage A or Stage B have the possibility to roll over to the OLE trial (see Section 5.6).

Additionally, at the time of the 88th event, patients in run-in will also be given the option to roll over to the OLE trial after performing an early discontinuation visit.

Patients who are defined as a non-responder during Stage A and/or discontinue the trial will be treated as considered appropriate by the investigator (see Section 7.5).

8. DISCONTINUATION OF IMP AND PATIENT DISCONTINUATION/WITHDRAWAL

Patients will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any discontinuation/withdrawal must be fully documented in the eCRF and source documents, including the reason (if stated), and should be followed up by the investigator.

Patients can have a temporary treatment discontinuation (see Section 8.1), a premature permanent treatment discontinuation (see Section 8.2), or can withdraw from further trial participation (see Section 8.3).

For premature permanent treatment discontinuation and withdrawal from further trial participation, the following general rules apply:

- As far as possible, any withdrawal of a patient should be decided after consultation with the medical monitor, who acts on behalf of the sponsor. However, withdrawal remains at the discretion of the treating physician.
- The reasons for any withdrawal are to be fully documented in the eCRF.

The criteria for screening and randomization are to be followed explicitly. However, the development of a condition that would have prevented a patient's entry into the trial according to the selection criteria is not a reason per se for withdrawal. If it is noted that a patient who does not meet 1 or more of the inclusion criteria and/or meets 1 or more of the exclusion criteria is inadvertently dosed, the medical monitor at the sponsor's designated CRO and the sponsor's medical director must be contacted immediately.

If a patient has failed to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In particular, attempts should be made to contact the patient to determine whether or not the reason for not returning is an AE. Likewise, if a patient declares his/her wish to discontinue from the trial, eg, for personal reasons, an attempt should be made to establish whether or not the true reason is an AE (bearing in mind that the patient is not obliged to state his/her reasons).

8.1. Temporary Interruption of IMP

A patient who does not need to be permanently discontinued from treatment might have a temporary interruption from treatment up to 2 consecutive doses or not more than 10% of the total planned doses that should have been taken (see Section 7.3). This implies that a patient can miss 1 IMP dose during Stage A and up to 4 IMP doses during Stage B (but not more than 2 consecutive doses).

Patients who interrupted the trial medication for a longer time will be excluded from the per-protocol analysis.

Patients for whom treatment is temporarily interrupted will have to complete the assessments of the corresponding visit (see SoA in Section 1.3) unless they withdraw their consent.

8.2. Permanent Early Discontinuation of IMP

Permanent early discontinuation from treatment means that the patient stops receiving the ongoing IMP treatment and does not restart IMP treatment, however, informed consent is not withdrawn. These patients will continue to be followed up for safety and efficacy/disease severity in the trial according to the SoA for the remaining visits of Stage A (excluding the optional additional visit at A-V13) or the remaining visits of Stage B, whichever is applicable (see Section 1.3), including the safety follow-up visit in case IMP was stopped less than 28 days before the last trial visit. Note that patients with an early discontinuation from treatment during Stage A will not be randomized in Stage B. These patients will stop the trial at the End of Stage A visit. Furthermore, patients with an early discontinuation from treatment during Stage B will not be able to roll over to the OLE trial (see Section 5.6).

A patient **must** be permanently discontinued from further trial medication in the event of any of the following:

- If in the opinion of the investigator and/or sponsor, the discontinuation of the IMP is necessary for the patient's safety.
- Patient develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion, or an AE of CTCAE grade 4 that is considered related to IMP by the sponsor.
- Use of non-permitted concomitant drug, as defined in Section 7.4.2.
- Psychiatric conditions.

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

Withdrawal from the trial is mandatory in case of meeting any of the withdrawal criteria (see Section 8.3 'Early Withdrawal From the Trial').

A patient **may** discontinue receiving clinical trial medication under the following circumstances:

- In case the patient has clinical evidence of bacterial, viral or fungal disease or any other significant disease which could confound the results of the trial or put the patient at undue risk. In this situation, decision on whether or not to discontinue patients early from treatment will depend on the evaluation on a case by case basis, which should be taken after discussion with the medical monitor. Patients who, after evaluation of the above situations, are not discontinued from treatment, may have a temporary interruption from treatment (see Section 8.1).

If permanent discontinuation from IMP occurs, the patient will be encouraged to continue with trial-related assessments for the remaining visits of Stage A (excluding the optional additional visit at A-V13) or the remaining visits of Stage B, whichever is applicable, according to the general SoA (see Section 1.3), including the safety follow-up visit in case IMP was stopped less than 28 days before the last trial visit. No Early Discontinuation visit should be conducted unless the patient requests to withdraw from the trial or in case of deterioration (see Section 2.2 and Section 8.3).

It is not mandatory to withdraw the patients from the trial, if withdrawal criteria are not met (see Section 8.3).

8.3. Early Withdrawal From the Trial

Early withdrawal from the trial is defined as the permanent cessation of further participation in the trial prior to its planned completion.

Patients are free to discontinue the trial at any time without giving their reasons.

A patient **must** be withdrawn from further trial participation in the event of any of the following:

- Withdrawal of the patient's consent.
- A patient's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this in the eCRF.
- The IMP treatment code is broken.
- Occurrence of pregnancy.
- The investigator, after discussion with the sponsor's medical director, deems it is in the patient's best interest.
- Death or lost to follow-up.
- For patients who permanently discontinued IMP and continue their current stage of the trial: In case they deteriorate (defined as an increase of adjusted INCAT score with respect to baseline of their current stage; see Section 2.2).
- (During Stage A only:) Adjusted INCAT deterioration of ≥2 points from Stage A baseline (D1A).

In case of premature withdrawal from the trial, all trial assessments scheduled for the Early Discontinuation visit (see Section 1.3) shall be performed, if possible, preferably immediately after the patient's last administration of trial drug, and all efforts should be made that the patient will have a final follow-up visit 28 days after the last IMP dose. The treating physician will then offer the patient the best available alternative treatment. In any case, the appropriate eCRF section must be completed.

The primary reason for discontinuation must be recorded in the appropriate section of the eCRF and all efforts must be made to complete and report the assessments as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made and any AEs should be followed up until resolution.

A termination eCRF page should be completed for every patient who receives investigational product, whether or not the patient completes the trial. The reason for any early discontinuation should be indicated on this form.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.4. Replacement

Patients, who prematurely discontinued from the trial after having received trial treatment, will not be replaced and their unique identification and treatment randomization numbers will not be reallocated.

8.5. Re-screening

Patient who withdrew from the trial during the screening or run-in phase and before the trial medication was started may be re-screened once if in the opinion of the investigator the patient would benefit from the trial treatment and the withdrawal reasons or criteria no longer apply, and permission has been granted by the medical monitor.

8.6. Lost to Follow-up

A patient will be considered lost to follow-up if he or 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 patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered withdrawn from the trial.

Discontinuation of specific sites or of the trial as a whole are handled as part of Appendix 1 (see Section 11.1.10).

9. TRIAL ASSESSMENTS AND PROCEDURES

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. When a protocol-required procedure cannot be performed, the investigator will document the reason and any corrective and preventive actions that he/she has taken to ensure that the normal processes are adhered to in the source documents. The trial team should be informed of these incidents in a timely manner.

Patients should be seen for all visits on the designated days or as closely as possible to the original planned visit schedule.

The timing of all trial procedures is provided in the SoAs in 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 patient should continue or discontinue IMP. 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 patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

A re-test in case of an out-of-range clinical laboratory test value to determine a patient's eligibility is allowed at the discretion of the investigator and in agreement with the sponsor.

The maximum amount of blood collected from each patient over the duration of the trial, including any extra assessments that may be required, will be approximately 500 mL (with a maximum of 40 mL per trial visit).

At each trial visit, all assessments as listed in the SoA in Section 1.3 should be completed before IMP administration at the site.

9.1. Serology Testing for Infections at Screening

At screening, an assessment is made if patients have clinical symptoms and/or signs of an active infection. These patients **cannot** be included in the trial (see exclusion criterion #7 in Section 6.2). Patients who might have serology results indicative of presence of microorganisms in the body, but who do not present evidence of an active infection, are not excluded. If an infection occurs during the trial, it shall be reported as an AE and treated accordingly. If deemed necessary, in selected cases, patients may be discontinued from the trial.

Specific attention is given to the following infections:

- Hepatitis B Virus (HBV):

  Patients with an active HBV infection (acute or chronic) at screening cannot be included in the trial. The following serologic combinations of serologic markers will be used to identify an active HBV infection (US Centers for Disease Control and Prevention):

HBsAg	Anti-HBc	Anti-HBs	Note
POSITIVE	POSITIVE	NEGATIVE	Acute or chronic active hepatitis B: patient cannot be enrolled in the trial
NEGATIVE	POSITIVE	NEGATIVE	Patient cannot be enrolled in the trial if considered to be an indicator of a ¨Low level" chronic infection with impairment of liver functions*

** As determined by a medical doctor with sufficient expertise in the field of hepatology or infectious diseases (may require performance of additional tests such as HBV viral load)*
Abbreviations: HBc = hepatitis B core; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen.

Patients who are seropositive because of an HBV vaccination or who are positive due to naturally recovered infection can be included.

- Hepatitis C Virus (HCV):

  Patients with an active HCV infection (acute or chronic) at screening cannot be included in the trial. The following serologic marker will be used to identify an active HCV infection (US Centers for Disease Control and Prevention):

HCV-Ab	Note
POSITIVE	Acute or chronic active hepatitis C: patient cannot be enrolled in the trial

Abbreviations: Ab = antibody; HCV = hepatitis C virus.

- Human Immunodeficiency Virus (HIV):

  HIV positive patients with no AIDS-defining condition* or CD4 count >200 cells/mm^3 can be included in the trial.

  HIV positive patients with an AIDS-defining condition* (or CD4 count ≤200 cells/mm^3) at screening cannot be included in the trial.

HIV	Clinical Condition or CD4 count	Note
POSITIVE	AIDS-defining condition* or CD4 count ≤200 cells/mm^3	Diagnosis of AIDS: patient cannot be included in the trial

* AIDS-defining conditions are defined as any of the following:
- Cytomegalovirus retinitis with loss of vision
- Pneumocystis Jiroveci Pneumonia
- Chronic Intestinal Cryptosporidiosis
- HIV-related encephalopathy
- Mycobacterium tuberculosis (pulmonary or extrapulmonary)
- Invasive cervical cancer

- Mycobacterium tuberculosis (TB):

  Patients with clinical symptoms/signs of TB cannot enter the trial. TB test (Quantiferon) will be performed at screening and may be repeated during the trial, if necessary. If a negative Quantiferon test at screening turns positive during the trial, a clinical work up will be applied. If clinical symptoms or signs of TB occur, it will be reported as an AE and treated accordingly.

9.1.1. Vaccination History and Vaccinations During the Trial

At screening, the investigator will ask the patient about all vaccination received in the past. Any vaccination information the patient or caregiver can remember should be recorded in the eCRF (with the brand name of the vaccine and date of vaccine administration recorded, if possible). If in the past a same vaccine was received more than once, including as booster, only the last one is to be collected. Any vaccination received during the trial, including administration date and brand name, will be entered as concomitant medication (see Section 7.4).

For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial (see Section 11.2).

9.2. Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening

At screening, suicidality will be assessed using the Columbia-suicide severity rating scale (C-SSRS). The questionnaire is included in Section 11.11. Patients with a high suicide risk will be excluded from the trial. Patients with a high suicide risk are defined as patients 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 above 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.

During the trial, suicidality will be assessed by specifically answering 1 question from the PHQ-9 (Patient Health Questionnaire-9) depression questionnaire (see Section 9.15).

9.3. Medical History

Clinically significant findings and pre-existing conditions present in a patient prior to screening must be reported on the relevant medical history/current medical conditions page of the eCRF.

Information should be provided on medical and surgical history and concomitant medical conditions specifying those ongoing at screening.

9.4. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA in Section 1.3.

During all visits, the efficacy assessments should be performed first, before any other trial-specific procedure, except for the ICF process during screening.

Where required, training will be provided for the efficacy instruments.

9.4.1. Adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score

The INCAT score (see Section 11.7) is a 10-point scale that covers the functionality of legs and arms and has been successfully used to measure treatment effects in various CIDP trials. Scores for arm disability range from 0 ("No upper limb problems") to 5 ("Inability to use either arm for any purposeful movement"), and scores for leg disability range from 0 ("Walking not affected") to 5 ("Restricted to wheelchair, unable to stand and walk a few steps with help"). The INCAT (total) score is the sum of these 2 scores and ranges from 0 to 10. For the "adjusted" INCAT

score, changes in the function of the upper limbs from 0 (normal) to 1 (minor symptoms) or from 1 to 0 will not be recorded as deterioration or improvement because these changes are not considered clinically significant.

There are 3 different baseline INCAT scores during the trial, at the beginning of each stage. Each baseline INCAT score is always the total INCAT score (not the adjusted INCAT score, which is used for post-baseline assessments):

- Baseline run-in period = Total INCAT score at the first visit of the run-in period (RI-V1)
- Baseline Stage A = Total INCAT score at D1A (ie, the first visit of Stage A [A-V1])
- Baseline Stage B = Total INCAT score at D1B (ie, the first visit of Stage B [B-V1])

Note: The baseline total INCAT score is calculated as the sum of the arm and leg sub score, without adjustment of the arm sub score.

For the post-baseline visits, the adjusted INCAT score calculation is based on the baseline of the corresponding stage.

Sites are selected based on their documented experience and expertise in the use of the assessments and questionnaires used in this trial. All sites will have a document knowledge and recent experience in the use of INCAT.

9.4.2. Medical Research Council (MRC) Sum Score

The 6-point MRC sum score evaluates motor strength/weakness (see also Section 11.8):

- 0= complete paralysis
- 1= minimal contraction
- 2= Active movement with gravity eliminated
- 3= Weak contraction against gravity
- 4= Active movement against gravity and resistance
- 5= Normal strength

The MRC Sum Score is evaluated bilaterally on 6 muscle groups of upper and lower limbs in order to obtain a summed score between 0 and 60:

- Arm abductors
- Elbow flexors
- Wrist extensors
- Hip flexors
- Knee extensors
- Foot dorsiflexors

9.4.3. Inflammatory Rasch-built Overall Disability Scale (I-RODS)

The I-RODS (see Section 11.9) is a PRO measure on disability and assesses the limitations of activities and social participation in patients with inflammatory neuropathies like Guillain-Barré syndrome (GBS), CIDP, and gammopathy-related polyneuropathy (MGUSP). The I-RODS is a 24-item scale, with each item representing a common daily activity that range from very difficult to do, like running or dancing, to very easy to do, like eating or reading a book. Higher scores indicate less disability. The raw sum scores of the I-RODS (range: 0 to 48) will be converted to a centile metric score, ranging from 0 (most severe activity and social participation restrictions) to 100 (no activity and social participation limitations).[19]

Although the I-RODS as a PRO can be considered subjective, the scale has shown to correlate well with grip strength, which is a direct measure of muscle strength.[20]

When assessed at home, the patient will record the measurements.

9.4.4. Mean Grip Strength

A handheld Martin vigorimeter will be used for this assessment. Patients will perform 3 assessments for each hand in an arbitrary order (with a rest period of approximately 30 seconds between each assessment) always at approximately the same time during the day. The mean grip strength for each hand will be used to determine disease activity.

When assessed at home, the patient will record the measurements.

9.4.5. Timed Up and Go (TUG) Test

The TUG test is a simple test used to assess a person's mobility and requires both static and dynamic balance.[21]

In the TUG test, the time expended to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down is measured. During the test, the person is expected to wear their regular footwear and use any mobility aids that they would normally require.

9.5. Safety Assessments

Planned time points for all safety assessments are provided in the SoA in Section 1.3.

9.5.1. Vital Signs and Physical Examination

The assessment of vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) will be performed at the time points indicated in the SoA (see Section 1.3). Vital signs will be measured before blood collections.

Blood pressure (systolic and diastolic) and heart rate will be measured using standard equipment in semi-supine position after having rested for at least 5 minutes.

It is recommended that the method used to measure body temperature at screening is maintained throughout the trial for each patient.

A physical examination will include at a minimum an assessment of general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological system.

Height will be measured at screening only and weight will be measured at screening and during the trial as indicated in the SoA (see Section 1.3). For the assessment of height and weight,

patients will be required to remove their shoes and wear light indoor clothing. Unintentional weight loss of >10% of normal body weight over a period of 6 months or less should be reported as an AE. 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.

9.5.2. Electrocardiograms

At screening and during the trial (as indicated in the SoA in Section 1.3), 12-lead ECGs will be recorded with the patient in a supine position, suitably rested (for at least 5 minutes).

At screening and baseline of Stage A (D1A), triplicate 12-lead ECGs will be performed before administration of the first dose of IMP; the results should be reviewed by the investigator to confirm that the patient may be dosed (see exclusion criteria in Section 6.2). A local cardiology consult should be sought if the investigator deems it necessary.

ECGs will be acquired according to instructions provided by a centralized ECG reading facility where the ECGs will be centrally assessed. At a minimum, interval data (PR, QT, QTcF [Fridericia corrected QT interval], and QRS intervals), ventricular rate, and overall interpretation will be recorded for each ECG. Data will be transferred electronically for inclusion in the database.

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.

9.5.3. Clinical Safety Laboratory Assessments

Blood and urine samples for safety assessments (hematology, biochemistry, and urinalysis) will be taken at screening, on D1A before IMP dosing, and further during the trial as specified in the SoA in Section 1.3. See Section 11.2 for a list of clinical laboratory tests to be performed.

Blood and urine samples for clinical chemistry, hematology, urinalysis, and serology testing will be collected according to the local standard procedures.

The samples will be analyzed at a centralized certified laboratory. In the exceptional circumstances that samples cannot be sent to a central laboratory, a local laboratory can be used.

Further details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual. The actual sample collection date and time will be collected. The fasting status will also be collected. If the glucose or lipids results from the screening visit are elevated, a repeat sample under fasting condition (for at least 8 hours) will be required.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial, with the exception of total protein and albumin results after the Stage B baseline visit, which will be kept blinded for the site. A system will be implemented to notify the investigator in case of out-of-range values to allow for appropriate safety follow-up.

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.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. These additional samples will be analyzed centrally, too. Only laboratory testing needed for the assessment of a specific AE/SAE, which is not already foreseen in the laboratory test battery, will be analyzed locally. Such a request and the medical need has to be discussed a priori with the medical monitor. The results of this local testing will be added to the AE/SAE follow-up documentation.

For all female patients of childbearing potential, a serum pregnancy test will be performed centrally at screening, and a urine pregnancy test will be conducted and analyzed locally at the site (on the urine samples taken for urinalysis) every 4 weeks during the rest of the trial.

Besides the urine pregnancy test and additional safety samples performed at the discretion of the investigator which will be conducted and analyzed locally, all samples for safety assessments will be analyzed centrally.

9.6. Adverse Events and Serious Adverse Events

AEs, defined in Section 11.4, will be reported by the patient and/or by the investigator. The treating physician (see Section 5.4.1 for the two physician concept) and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE (see Section 11.4) and remain responsible for following up AEs that are serious, considered related to IMP administration or trial procedures, or that caused the patient to discontinue the IMP or the trial (see Section 8). These AEs will be monitored until stabilization, resolution, or loss to follow-up (for serious events, SAE forms need to be completed; see Section 11.4).

9.6.1. Pregnancy

All initial reports of pregnancy in female patients and in female partners of male patients who participate in the trial will be collected after the first administration of IMP (Stage A baseline [D1A]) until the last trial visit.

Note that in this trial patients must comply with recommendations for contraceptive use in order to avoid exposure to IMP of an existing embryo/fetus to IMP (see inclusion criteria in Section 6.1).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and will contact the patient at the expected time of delivery for follow-up. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormality, ectopic pregnancy, birth defect) will be considered SAEs and will be reported as such.

9.6.2. Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI, which can be serious or non-serious, and/or related or not related) is 1 of scientific and medical concerns specific to the sponsor’s product or program (eg, underlying condition being investigated, mechanism of action/potential immunosuppression), for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with the reduction in IgG levels. The occurrence of an infection will be an AESI. This interest pertains to both newly diagnosed or reactivated, latent infections. Hereby any occurrences of an infection will have to be reported accordingly.

9.7. Medication Error

For this trial, a variation less than ±10% of the amount of efgartigimod PH20 SC that should be injected for each administration will not be considered an overdose/underdose or medication error, while a variation greater than ±10% of the intended amount of efgartigimod PH20 SC will be considered a medication error and/or overdose with or without AEs.

A patient must not miss more than 2 consecutive doses and must not miss more than 10% of the total planned doses that should have been taken. Furthermore, 2 consecutive doses should be given with an interval of at least 3 days (see Section 7.3).

An overdose is defined as a deliberate or accidental administration of IMP to a patient, at a dose greater than that which was assigned to that patient per the trial protocol.

A medication error is any preventable incident that may cause or lead to inappropriate IMP use or patient harm 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 patient should 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 should be documented in the eCRF including the additional AE, if any.

9.8. Patient Card

Patients must be provided with the address and telephone number of the Treating Physician, and of the main contact for information about the clinical trial. The investigator must therefore provide a "Patient Card" to each patient. In an emergency situation this card serves to inform the responsible attending physician that the patient is in a clinical trial and that relevant information may be obtained by contacting the investigator or sponsor designee. Patients must be instructed to keep the card in their possession at all times.

9.9. Pharmacokinetics

Blood samples for determination of serum concentrations of efgartigimod will be collected from D1A pre-dose onwards and at certain time points up to the follow-up visit as specified the SoA in Section 1.3.

Blood for the PK samples will be collected as described in the laboratory manual. Blood samples may also be used to cross-validate the PK assay in CIDP matrix (serum).

Concentrations of efgartigimod in serum will be determined using a validated assay.

9.10. Pharmacodynamics

Blood samples for determination of total IgG in serum will be taken at several time points during the trial from D1A pre-dose onwards as indicated in the SoA in Section 1.3.

Blood for the PD samples will be collected as described in the laboratory manual. Blood samples may also be used to cross-validate the PD assays in CIDP matrix (serum).

Note that local IgG testing must not be performed.

9.11. Genetics

Not applicable.

9.12. Biomarkers

See Section 9.10 for the collection of PD samples to measure total IgG.

[redacted]

Samples may be stored for up to 15 years, unless this would not be allowed according to local regulations or the patient would not agree.

9.13. Immunogenicity Assessments: Anti-drug Antibodies (ADA)

Samples for determination of anti-drug antibodies (ADA) against efgartigimod (measured in serum) and antibodies against rHuPH20 (measured in plasma) will be taken prior to dosing on Stage A baseline (D1A) and before the SC injection of IMP at several time points as indicated in the SoA in Section 1.3.

Titers of binding antibodies (BAb) and the presence of neutralizing antibodies (NAb) against efgartigimod will be measured in serum. Titers of BAb and NAb against rHuPH20 will be measured in plasma. NAb will be tested for all confirmed positive ADA samples.

Blood for the immunogenicity samples will be collected as described in the laboratory manual. Blood samples may also be used to cross-validate the ADA and NAb assays in CIDP matrix (serum and plasma).

9.14. Additional Patient-reported Outcome (PRO) Tools

Additional PRO data, associated with medical encounters, are measured at Stage A baseline (D1A) and at several time points during the trial as indicated in the SoA in Section 1.3 and will be collected in the CRF by the investigator and trial-site personnel for all patients. Protocol-mandated procedures, tests, and encounters are excluded.

[redacted]

The data collected are based on the PROs of the questionnaires described below.

9.14.1. EuroQol 5 Dimensions and 5 Levels Health-related Quality-of-Life Questionnaire (EQ-5D-5L)

Quality of life will be assessed through the EQ-5D-5L, which allows responses recording based on 5 levels of severity.[22] It is a standardized instrument for use as a measure of health for clinical and economical appraisal.

[redacted]

[redacted]

9.15. Suicidality Assessment During the Trial

A prospective assessment for suicidal ideation and behavior is included in this clinical trial, as recommended for trials involving a biological product for a neurological indication.[31]

At screening, patient's suicidality will be assessed via the Columbia-suicide severity rating scale (C-SSRS); patients with a high suicide risk cannot enter the trial (see Section 9.2).

During the trial, the suicidality assessment will be conducted by specifically answering the following question, derived from the 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 patient will be asked this question at each visit after screening 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.[32]

10. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by the sponsor's designated CRO using statistical analysis systems SAS® (SAS Institute, Cary, NC, US) version 9.4 or higher, and the software package R, if applicable. The standard operating procedures (SOPs) and work instructions of the sponsor's designated CRO will be used as the default methodology if not otherwise specified.

A detailed and comprehensive Statistical Analysis Plan (SAP) will be written and signed-off prior to final analysis database lock. For the Stage A interim analysis (see Section 10.6), a separate stand-alone interim SAP will be written and signed-off prior to interim database lock.

Minor changes to the statistical methods set out in this protocol do not require a protocol amendment but must be documented (as changes from the protocol) in the SAP and in the trial report(s).

The final statistical analyses will be performed once all patients have rolled over to the OLE trial ARGX-113-1902 or have withdrawn, and the database has been cleaned and locked.

10.1. Statistical Methods

10.1.1. Summary Tables, Figures, and Listings

Summary tables will summarize endpoints (outcomes) by treatment group and time point (eg, visit). For continuous variables, the number of patients (with non-missing values), mean, standard deviation, median, quartiles, minimum and maximum will be presented. For categorical variables, for each category, the number of patients (count) and percentage will be presented for patients without missing values.

All summary Tables and Figures will be supported by full patient listings.

10.1.2. Hypothesis Testing and Confidence Intervals

Unless otherwise stated, all statistical tests will be two-sided and will be conducted at a 5% significance level. Two-sided 95% confidence intervals (CIs) will be provided.

10.1.3. Populations for Analyses

Safety population: The Stage A safety population (SAF-A) will include all patients who received at least 1 dose of IMP in Stage A. The Stage B safety population (SAF-B) will include all patients who received at least 1 dose of IMP in Stage B.

The safety data analysis will be presented as follows:

- Stage A will be done on the Stage A safety population (SAF-A).
- Stage B will be done on the Stage B safety population (SAF-B).
- Stages A and B combined on the Stage A safety population (SAF-A).
- Stages A and B combined on the Stage B safety population (SAF-B).

Pharmacokinetic population: The PK population will include all patients in the safety population for whom at least 1 serum PK concentration is available.

Pharmacodynamic population: The PD population will include all patients in the safety population for whom at least 1 serum PD concentration is available.

Immunogenicity population: The immunogenicity population will include all patients in the safety population for whom at least 1 ADA sample is available.

Modified intent-to-treat (mITT) population: The mITT population will include all randomized patients who received at least 1 dose of IMP in Stage B.

Per protocol (PP) population: The PP population comprises all Stage B patients in the mITT population for whom no major protocol deviation was reported.

The efficacy analyses for the Stage B will be based on the mITT population. Supportive analyses for the primary endpoint will be conducted on the PP population.

The Stage A efficacy analysis will be conducted on the Stage A safety population (SAF-A).

10.1.4. Randomization and Stratification

Stage A is non-randomized; all patients will receive efgartigimod PH20 SC in an open-label manner.

In Stage B, patients will be randomized to double-blind efgartigimod PH20 SC or placebo in a 1:1 ratio. Patients will be stratified according to their prior CIDP medication and the decrease of adjusted INCAT score during Stage A by the following:

- Prior CIDP medication
  - Treatment-naïve (see inclusion criterion #6 in Section 6.1 for definition);
  - Pulsed corticosteroid treatment or oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day;
  - IVIg or SCIg treatment.
- Adjusted INCAT score
  - No change in adjusted INCAT score during Stage A;
  - Adjusted INCAT score decrease of ≥1 point during Stage A.

The randomization list for Stage B will be created using permutated blocks and implemented using the IRT.

10.1.5. General Considerations

10.1.5.1. Trial Baselines

The baseline value for the run-in period will be the assessment recorded at visit R1-V1.
The baseline value for Stage A will be the last assessment prior to the first dose of open-label trial medication in Stage A.

The baseline value for Stage B will be the last assessment prior to the first dose of double-blind trial medication in Stage B.

10.1.5.2. Visits and Dates

All trial visits will be recalculated based on actual dates and will be referred to as “analysis visits” which will be used in the statistical analyses. The rules for calculating the analysis visits

will be documented in the SAP. The actual visit recorded in the database and the analysis visits will be presented in the listings.

Rules for imputing partial dates or missing dates will also be documented in the SAP.

10.1.6. Blinded Data Review Meeting

A blinded data review meeting will be convened after the data has been cleaned but before the final lock and unblinding. A data review meeting will also be convened before the interim analysis database lock. The review will be performed per the requirements of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline E9.[33]

10.2. Statistical Hypotheses

The statistical hypotheses were derived from the trial objectives as stated in Section 4.

Stage A:

- For the interim analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact one-sided Clopper-Pearson 90% CI. For the final analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact Clopper-Pearson 2-sided 95% CI. This 95% two-sided Clopper-Pearson CI will be used to compare the results of this study with results obtained in historical controls such as the PATH trial (van Schaik et al, 2018)[15]

Stage B:

- Null hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is 1 (ie, hazard ratio = 1)
- Alternative hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is ≠1 (ie, hazard ratio ≠1)

As Stage A and Stage B testing will be on different populations, adjustments for multiplicity do not need to be made.

10.3. Sample Size Determination

If it is hypothesized that the event rate of efgartigimod PH20 SC to placebo is 0.50 (ie, hazard ratio of 0.50), then 88 events are required to provide 90% power at a 1-sided alpha level of 0.025 using a log-rank test. An event is defined as an adjusted INCAT increase during Stage B (an increase [worsening] of 1 point will need to be confirmed at a consecutive visit 3-7 days after the first adjusted INCAT score increase of 1 point. For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required; see Section 2.2). The events will be monitored in a blinded way to ensure the trial is sufficiently powered. The table below shows the expected sample size for different scenarios for median time to event for the placebo arm, assuming a 48-week maximum follow-up period for each patient, an accrual rate of 4 patients per month during the first 6 months and an accrual rate of 7.8 patients per month thereafter. To obtain a sufficient number of patients randomized into Stage B, up to approximately 360 patients would be required to be enrolled into Stage A. Patients

will continue to be randomized into Stage B until 88 events are observed as per the sample size calculation, the trial will end when the 88th event is observed.

Median Time to Event[a] for Placebo	Expected Sample Size for Stage B
1 month	96 patients
2 months	107 patients
3 months	119 patients
4 months	132 patients
5 months	146 patients
6 months	159 patients
7 months	173 patients
8 months	186 patients

[a] Event = increase in adjusted INCAT score relative to Stage B baseline in the adjusted INCAT score (see Section 2.2).

10.4. Endpoints

The endpoints of the trial are separated into 2 periods according to the 2 defined trial stages.

10.4.1. Stage A

10.4.1.1. Primary Endpoint:

- Percentage of patients with confirmed ECI during Stage A

10.4.1.2. Secondary Endpoints for Evidence of Clinical Activity

- Time to initial confirmed ECI during Stage A.
- Change from Stage A baseline (D1A) over time during Stage A in:
  - Adjusted INCAT score
  - MRC Sum score
  - 24-item I-RODS disability scores
  - TUG score
  - Mean grip strength assessed by Martin vigorimeter

10.4.1.3. Secondary Endpoints for Safety

- Exposure adjusted occurrence of TEAEs and SAEs by SOC and PT during Stage A
- Incidence of clinically significant laboratory abnormalities during Stage A

10.4.1.4. Secondary Endpoint for PK

- Pre-dosing efgartigimod serum concentrations over time during Stage A

10.4.1.5. Secondary Endpoint for PD

- Changes of serum IgG levels (total IgG) over time during Stage A

10.4.1.6. Secondary Endpoint for Immunogenicity

- Percentage of patients with and titers of binding antibodies (BAb) toward efgartigimod and/or rHuPH20 during Stage A. Presence of neutralizing antibodies (NAb) against efgartigimod and titers of NAb against rHuPH20 during Stage A

10.4.1.7. Secondary Endpoint for PRO:

- Changes from D1A in EQ-5D-5L over time during Stage A

10.4.2. Stage B

10.4.2.1. Primary Endpoint

- Time to first adjusted INCAT deterioration compared to Stage B baseline (defined by the time from first dose of double-blind IMP to the first adjusted INCAT deterioration compared to Stage B baseline; see Section 2.2)

10.4.2.2. Secondary Endpoints for Efficacy

- Time to CIDP disease progression (defined by the time from first dose of double-blind IMP to the first I-RODS score decrease ≥4 points compared to Stage B baseline using the centile metric)
- Percentage of patients with improved functional level compared to Stage B baseline as measured by an increase in the 24-item I-RODS score up to week 48
- Change from Stage B baseline over time in:
  - Adjusted INCAT score
  - MRC Sum score
  - 24-item I-RODS disability scores
  - TUG score
  - Mean grip strength assessed by Martin vigorimeter
- Change from Stage A baseline over time for subjects randomized to efgartigimod PH20 SC in:
  - Adjusted INCAT score
  - MRC Sum score
  - 24-item I-RODS disability scores
  - TUG score
  - Mean grip strength assessed by Martin vigorimeter
- Time to 10% decrease in the 24-item I-RODS during Stage B

10.4.2.3. Secondary Endpoints for Safety

- Incidence of TEAEs and SAEs by SOC and PT during Stage B
- Incidence of clinically significant laboratory abnormalities during Stage B

10.4.2.4. Secondary Endpoint for PK

- Pre-dosing efgartigimod serum concentrations over time during Stage B

10.4.2.5. Secondary Endpoint for PD

- Changes of serum IgG levels (total IgG) over time during Stage B

10.4.2.6. Secondary Endpoint for Immunogenicity

- Percentage of patients with and titers of binding antibodies (BAb) toward efgartigimod and/or rHuPH20 during Stage B. Presence of neutralizing antibodies (NAb) against efgartigimod and titers of NAb against rHuPH20 during Stage B

10.4.2.7. Secondary Endpoint for PRO:

- Changes from Stage B baseline in EQ-5D-5L over time during Stage B

10.4.3. Exploratory Endpoints

10.5. Statistical Analyses

The SAP will be finalized before database lock 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 key secondary endpoints.

For the Stage A interim analysis (see Section 10.6 for details), a separate stand-alone interim SAP will be written and signed-off prior to interim database lock.

10.5.1. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics data, including prior and concomitant therapies, will be summarized using standard summary statistics (see Section 10.1.1).

10.5.2. Patient Disposition

Patient disposition and withdrawals will be fully accounted for in a summary. The number of patients entering and leaving each phase of the trial will be clearly indicated and where relevant will be presented by treatment group. The major reason for discontinuation will also be given by stage and where relevant by treatment group.

10.5.3. Populations for Analyses and Protocol Deviations

The number of patients for each population for analysis, as described in Section 10.1.3, will be presented in a table and listing.

Major protocol deviations, by treatment group and trial stage, will be summarized in a table and presented in a listing.

10.5.4. Efficacy Endpoints

10.5.4.1. Stage A: Confirmed ECI

For the interim analysis, the proportion of patients with confirmed ECI will be calculated with the exact Clopper-Pearson 90% 1-sided lower CI. For the final analysis, the proportion of patients with confirmed ECI will be calculated using an exact Clopper-Pearson 2-sided 95% CI.

10.5.4.2. Stage A: Evidence of Clinical Activity Time

A Kaplan-Meier table and graph will be presented for the clinical activity time to initial confirmed improvement. No formal statistical analysis will be present as Stage A only has 1 treatment group. However, the Kaplan-Meier table and graph will present CIs.

10.5.4.3. Stage B: Adjusted INCAT Score

The primary endpoint of time to clinical deterioration (defined as the time from first dose of double-blind trial medication to the first adjusted INCAT deterioration compared to Stage B baseline; see Section 2.2) will be analyzed via Cox regression modeling in the mITT population. Patients without clinical deterioration will be censored at their last follow-up visit. The analysis will be stratified for randomization stratification factors (see Section 10.1.4). A fixed effect term will be included as a covariate for randomized treatment. The hazard ratio will be estimated from

the model along with the associated 95% CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and median times to clinical deterioration will be estimated.

As the endpoint is a time to event, missing data methods will not be used as all patients will have a last know visit (including at minimum randomization) at which they can be censored.

The primary analysis will only consider deterioration through the adjusted INCAT score. Patients who withdraw will be censored at the time of withdrawal. The effect of withdrawals and other factors will be investigated as part of the sensitivity analysis which will be documented in the SAP.

10.5.4.4. Stage B: I-RODS Score

The time to CIDP disease progression (defined by I-RODS deterioration) during Stage B up to week 48 will be analyzed using the same Cox's model as for the adjusted INCAT score (see Section 10.5.4.3).

The percentage of patients with improved functional level (compared to Stage B baseline) as measured by the I-RODS score during Stage B up to week 48 will be analyzed by exact logistic regression. A fixed effect term will be included for randomized treatment and I-RODS score at end of Stage A will be included as a covariate. The odds ratio will be estimated from the model along with the associated 95% CI and 2-sided p-value. Exact Clopper-Pearson 2-sided 95% CI limits will be calculated for the proportion of patients with disease progression in each arm.

10.5.5. Stage A and Stage B: Other Efficacy and PK, PD, and Immunogenicity Endpoints

Descriptive statistics will be provided for efficacy endpoints other than described above (clinical functional assessments of motor function and muscle strength, and PROs) and for PK, PD, and immunogenicity data.

10.5.6. Stage A and Stage B: PRO EQ-5D-5L Endpoint

EQ-5D-5L scores and changes from baseline (ie, changes from D1A over time during Stage A and changes from Stage B baseline over time during Stage B) will be presented using standard summary statistics.

10.5.7. Stage A and Stage B: Safety Endpoints

Summaries AEs and other safety parameters will be provided for Stage A, Stage B (by treatment arm), and Stage A and B combined (for efgartigimod PH20 SC treatment).

AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. AEs reported from the first dose of trial drug until 30 days after the last dose of trial drug will be considered as TEAEs and will be summarized descriptively. TEAEs (including AESIs) will be listed corresponding to system organ class and MedDRA preferred term. Patients with multiple occurrences of events will only be counted once at the maximum severity/grade to trial drug for each PT, SOC. The severity will be assessed using the common terminology criteria for AEs (CTCAE) (see Section 11.4). Any AEs with missing severity or relationship to trial drug will be classified as severe and treatment-related, respectively. All AEs will be summarized by relatedness to trial medication. Any AEs leading to death or discontinuation of trial medication will also be summarized.

Laboratory and vital sign parameters and their respective changes from baseline will be presented using standard summary statistics (see Section 10.1.1). Clinically significant laboratory abnormalities will also be summarized descriptively.

10.5.8. Exploratory Endpoints

Analyses of exploratory endpoints [redacted]) may be performed at a later stage than the analyses of the other endpoints and may be described in a separate SAP and in another report than the main CTR.

10.6. Interim Analyses

After the first 30 patients have reached the end of Stage A, an interim analysis will be performed and the proportion of patients with confirmed ECI will be calculated with the exact Clopper-Pearson 90% 1-sided lower CI. A non-binding futility rule will be used to guide continuation of the study. If 9 or less of the first 30 subjects have a confirmed ECI, the Clopper-Pearson 90% 1-sided lower CI will not exclude a rate of 21%, (placebo rate observed in ICE trial[16]), and the recommendation will be to stop the trial. The DSMB charter will contain full details on the non-binding futility rule and guidance to continue the trial. The decision to continue the trial will be advised by an independent DSMB (see Section 11.1.5) and the final decision will be taken by the sponsor.

Activity, PD, PK, immunogenicity, and safety data will be presented descriptively in the single-arm, open-label Stage A.

The planned interim analysis will be described in greater detail in the SAP.

10.7. Independent Data Safety Monitoring Board (DSMB)

Details on the DSMB are provided in Section 11.1.5 (Appendix 1).

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the current Declaration of Helsinki, the applicable guidelines for good clinical practice (GCP), or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

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 patients.

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 Title 21 of the Code of Federal Regulations (21 CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

11.1.2. 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.

11.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the patient and answer all questions regarding the trial.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that written informed consent was obtained before any screening assessment was performed and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current approved version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the patient.

A patient can be re-screened only if the patient has not started treatment in Stage A and with the sponsor's written approval.

11.1.4. Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain this identifier; patient names or any information that would make the patient identifiable will not be transferred.

The patient 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 patient who will be required to give consent for their data to be used as described in the informed consent.

The patient 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.

11.1.5. Independent Data and Safety Monitoring Board (DSMB)

An independent DSMB will be used in this trial.

The sponsor will appoint a DSMB consisting of an independent group of clinical experts, who are not participating in the trial. They will be supplemented by an independent statistician. The objective of the DSMB will be to review all unblinded safety data (including the overall number of patients treated up to that point, rates, and patient-level details). For Stage B, the DSMB will also determine if there is an imbalance in the treatment arms with respect to these events, based on clinical judgment of the DSMB. Fixed meetings will be scheduled based on the achievement of 25%, 50% and 75% recruitment targets into the trial, and incidence of (S)AEs. In addition, ad hoc meetings can be requested at any time during the trial by either the sponsor or the DSMB. The DSMB will advise the sponsor concerning continuation, modification, or termination of the trial after every meeting.

The composition, objectives, and role and responsibilities of the DSMB will be described in a charter. The DSMB charter will also define and document the content of the safety summaries, and general procedures (including communications).

11.1.6. CIDP Confirmation Committee (CCC)

Misdiagnosis of CIDP has been reported to occur frequently among less experienced physicians. Therefore, in this trial the investigator's diagnosis of CIDP will be reviewed by an independent committee (ie, CCC) during the screening period. Patients for whom the diagnosis cannot be confirmed, will not be eligible to enter the trial.

The CCC will be composed of neurologists with at least 10 years of experience in the diagnosis of CIDP and a documented track record of at least 100 diagnosis of CIDP.

The CCC is responsible to ensure, that the CIDP trial population included in this trial is fulfilling the official EFNS/PNS 2010 diagnostic criteria.[2]
These are used to define probable or definitive progressing or relapsing forms of CIDP in which both sensory symptoms and limited motor functions, or limited motor functions only have to be present to qualify the patient to the trial.

A patient profile will be presented for CCC member review.

In case the information provided to the CCC is not sufficient to confirm a definite or probable CIDP diagnosis per the EFNS/PNS 2010 criteria,[2] additional assessments may be asked for (as listed in Section 11.5 Appendix 5) to support the confirmation of diagnosis.

A specific CCC Charter will describe the review process, which will be properly documented.

Each site will be instructed about the procedure of the review process.

11.1.7. Dissemination of Clinical Trial Data

All information regarding efgartigimod PH20 SC supplied by the sponsor to the investigator and all data generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The results of the trial will be reported in a CTR.

The CTR, written in accordance with the ICH E3 guideline, will be submitted in accordance with local regulations.

Any manuscript, abstract or other publication, presentation of results, or information arising in connection with the trial must be prepared in conjunction with the sponsor and must be submitted to the sponsor for review and comment prior to submission for publication or presentation. Trial patient identifiers will not be used in the publication of results.

Authorship will be granted according to the International Committee of Medical Journal Editors criteria, based on scientific input and recruitment efforts, and will be granted upon decision of a publication committee. This committee will include among others the coordinating investigator and the sponsor.

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

11.1.8. Data Quality Assurance

All patient data relating to the trial will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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 (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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical 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, CROs).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.

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.

11.1.9. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents will be filed at the investigator's site. These data are usually later entered in the eCRF.

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 Investigator Source Data Agreement Form describes the source data for the different data in the eCRF. This document should be completed and signed by the investigator, and should be filed in the investigator's trial file. Any data item for which the eCRF will serve as the source must be identified, agreed, and documented in the Investigator Source Data Agreement Form.

11.1.10. Trial and Site Start and Closure

The trial start date is the date on which the first patient signs the ICF in this trial.

The sponsor 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:

- 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 recruitment of patients by the investigator;
- Discontinuation of further IMP development.

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 patient and should assure appropriate patient therapy and/or follow-up.

11.2. Appendix 2: Clinical Laboratory Tests

Safety Laboratory Testing

Hematology

Red blood cell count	Hemoglobin	Hematocrit
Mean cell volume	Mean cell hemoglobin	Mean cell hemoglobin concentration
Red cell distribution width	Platelets	
White blood cell count	Lymphocytes count	Monocytes
Eosinophils	Basophils	Neutrophils count

Coagulation

International normalized ratio	Activated partial thromboplastin time	Prothrombin time

Blood Chemistry Tests

Glucose	Creatinine	Total protein[§]
Albumin[§]	Bilirubin	Alkaline phosphatase
Aspartate transferase	Alanine transferase	Gamma glutamyl transferase
Cholesterol*	High-density lipoprotein cholesterol*	Low-density lipoprotein cholesterol (LDL)*
Total cholesterol/HDL ratio*	Triglycerides*	Estimated glomerular filtration rate[#]
high-sensitive C reactive protein	Blood urea nitrogen	Hemoglobin A1c
Lactate dehydrogenase	Uric acid	Potassium
Sodium	Calcium	Serum pregnancy test*
Total immunoglobulin G (IgG)*		

* At screening visit only
§ In the exceptional circumstances that using a central laboratory is not possible: Do not measure total protein and albumin after the Stage B baseline visit.
# Chronic Kidney Disease – Improved Prediction Equations (CKD-EPI) will be used for estimating glomerular filtration rate; it will be reported as creatinine clearance.

Blood Screening for Infections

HIV[§] (Ag/Ab test)	Viral Hepatitis (HBsAg, anti-HBc Ab, Anti-HBs, Anti-HCV Ab [HCV RNA if reactive])	Tuberculosis (Quantiferon)

Abbreviations: Ab=antibody; Ag=antigen; HBc=hepatitis B core; HBs=hepatitis B surface; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

§ CD4 count to be analyzed in case of positive HIV (see exclusion criterion #7)

Urine Analysis	
Dipstick: pregnancy, pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity	In case of abnormal dipstick results*, light microscopy: erythrocytes, leucocytes, casts, and epithelial cells

* If urinary tract infection is suspected, investigations (such as microscopy, culture and sensitivity) should be performed locally by the investigator.

Investigators must document their review of each laboratory safety report.

Pharmacokinetic Analysis#
Serum concentrations of efgartigimod

Pharmacodynamic Analysis#
Concentrations of total IgG

Immunogenicity Analysis#
ADA (via ELISA) and NAb against efgartigimod (serum samples);
Antibodies and NAb against rHuPH20 (plasma samples)

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

In addition, serum samples will be stored for possible future analyses. These potential future analyses may include but will not be limited to the following: chemokines, cytokines, complement, protein expressions, and others.

Blood samples may also be used to cross-validate the PK, PD, biomarker and ADA assays in CIDP matrix (serum and plasma), as well as used for vaccination antibody testing.

11.3. Appendix 3: Contraceptive and Barrier Guidance

11.3.1. General Instructions and Definitions

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception.

Women of childbearing potential must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before IMP can be administered.

A woman is considered of childbearing potential unless she is either:

- Postmenopausal, 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.
- Surgically sterilized: Women who have had a documented permanent sterilization procedure (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

11.3.2. Female Contraception for Women of Childbearing Potential

Women of childbearing potential should use an acceptable method of contraception during the trial.

The following methods of contraception, described in the Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials,[34] are allowed in this trial:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

11.3.3. Male Contraception

An acceptable method of contraception is a condom.

11.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.4.1. Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical trial patient, temporally associated with the use of IMP, whether or not considered related to the IMP. 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 IMP.

Definition of Unsolicited and Solicited AE
An unsolicited AE is an AE that was not solicited using a Patient Diary and that is communicated by a patient who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The patient will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of patient's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the patient's records. Unsolicited AEs that are not medically attended nor perceived as a concern by the patient will be collected during interview with the patient and by review of available medical records at the next visit. Solicited AEs are predefined local (at the injection site) and systemic events for which the patient is specifically questioned, and which are noted by the patient in his/her diary.

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 conditions detected or diagnosed after signing the ICF even though it may have been present before the start of the trial. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP 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 by itself 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 an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT to be Collected as AEs

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient'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 patient's condition.

Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure during the trial 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.

11.4.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

- **Is life-threatening**

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the patient has been detained at 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 as 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 is not collected as an AE.

- **Results in persistent 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 experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations:**

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.4.3. 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, diagnostics reports, and autopsy reports) related to the event.

The investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the SAE coordinator/sponsor in lieu of completion of the AE/SAE CRF page or SAE form.

There may be instances when copies of medical records for certain cases are requested by eg, the SAE coordinator or the sponsor. In this case, all patient identifiers, with the exception of the patient 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 Event Severity

The investigator will make an assessment of severity for each AE and SAE reported during the trial.

All events (AEs and SAEs) observed will be graded using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0. 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 (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 selfcare activities of daily living (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.

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 IMP and each occurrence of each AE/SAE, using 1 of the following categories:

- Not related: events can be classified as "not related" if there is not a reasonable possibility that the IMP caused the AE.
- Unlikely related: an "unlikely" relationship suggests that only a remote connection exists between the IMP and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.
- Possibly related: a "possible" relationship suggests that the association of the AE with the IMP is unknown; however, the AE is not reasonably supported by other conditions.
- Probably related: a "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other

conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.

- Related: a "related" relationship suggests that the AE follows a reasonable temporal sequence from administration of IMP, it follows a known or expected response pattern to the IMP, and it cannot reasonably be explained by known characteristics of patient's clinical state.

In final evaluation for reporting, the assigned relationship, as per Council for International Organizations of Medical Sciences (CIOMS), will be converted into a "binary determination" as follows: Events with an assigned relationship of "unrelated" or "unlikely related" will be grouped into the "unrelated" category. Events with an assigned relationship of "related," "possibly related," or "probably related" will be grouped into the "related" category.

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.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator will also consult the IB 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 SAE coordinator/sponsor. However, it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the SAE coordinator/sponsor.

The investigator may change his/her opinion of causality in context 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

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the SAE coordinator/sponsor 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 patient dies during participation in the trial or during a recognized follow-up period, then the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology, if available.

New or updated information (eg, entry mistakes) will be recorded in the originally completed CRF until the lock of the database. Thereafter, new/updated information will be collected in the safety database at the SAE coordinator.

The investigator will submit any updated SAE data to the SAE coordinator within 24 hours of receipt of the information.

11.4.4. Reporting of SAEs and AESIs

SAE and AESI Reporting

- All SAEs and AESIs (Section 9.6.2) will be recorded (within 24 hours) on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form.
- The investigator or designated site staff will ensure all entered data are consistent.
- An alert email for the SAE and AESI reports on the eCRF will automatically be sent by email to the sponsor or designee's safety mailbox via the electronic data capture (EDC) system.
- The paper SAE report form will be faxed or emailed to the sponsor's designee (see the Serious Adverse Event Reporting details on the first page of this protocol).

11.5. Appendix 5: CIDP Diagnostic Tests

In the event that the CCC cannot confirm the CIDP diagnosis based on the data presented by the investigator, they can suggest additional evaluations according to the following table. Based on the table below, any finding suggestive of any concomitant disease should be investigated according to the investigator's clinical practice.

Investigations to be Considered to Confirm CIDP Diagnosis (Taken From EFNS/PNS 2010 Guideline,[2] Table 2, Illustrating the Good Practice Points):

To diagnose chronic inflammatory demyelinating polyradiculoneuropathy
Electrodiagnostic studies including sensory and motor nerve conduction studies, which may be repeated, performed bilaterally, or use proximal stimulation for motor nerves
CSF examination including cells and protein
MRI spinal roots, brachial plexus, and lumbosacral plexus
Nerve biopsy
To detect concomitant diseases
(a) Recommended studies
[a]Serum and urine paraprotein detection by immunofixation[b]
Fasting blood glucose
Complete blood count
Renal function
Liver function
Antinuclear factor
Thyroid function
(b) Studies to be performed if clinically indicated
[a]Skeletal survey
Oral glucose tolerance test
Borrelia burgdorferi serology
C reactive protein
Extractable nuclear antigen antibodies
Chest radiograph
Angiotensin-converting enzyme
HIV antibody
To detect hereditary neuropathy
Examination of parents and siblings
Appropriate gene testing (especially PMP22 duplication and connexin 32 mutations)
Nerve biopsy

[a] Repeating these should be considered in patients who are or become unresponsive to treatment.

[b] Immunofixation is not available in some participating countries of this study. In that case, serum protein electrophoresis can be used as the first screen. Any abnormalities detected in the immunoglobulin band will be further investigated using a local/internationally acceptable method.

11.6. Appendix 6: CIDP Disease Activity Status (CDAS)

The following CDAS classification is based upon the clinical assessment of the treating physician (taking into account the duration of the disease, clinical response, neurological examination status, and duration of treatment) (from Gorson et al, 2019[3]):

1. Cure: ≥5 years off treatment
   - A. Normal examination
   - B. Abnormal examination, stable/improving
2. Remission: <5 years off treatment
   - A. Normal examination
   - B. Abnormal examination, stable/improving
3. Stable active disease: ≥1 year, on treatment
   - A. Normal examination
   - B. Abnormal examination, stable/improving
4. Improvement: ≥3 months <1 year, on Treatment
   - A. Normal examination
   - B. Abnormal examination, stable/improving
5. Unstable active disease: abnormal examination with progressive or relapsing course*
   - A. Treatment naïve or <3 months
   - B. Off treatment
   - C. On treatment

The classification is based upon the clinical assessment of the treating physician at the time of last evaluation.
CDAS, CIDP disease activity status; CIDP, chronic inflammatory demyelinating polyneuropathy.
*5B and 5C refer to patients who were treatment refractory from prior therapy or worsening despite ongoing therapy.

11.7. Appendix 7: Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale

Arm disability (05)	0 = No upper limb problems 1 = Symptoms, in 1 or both arms, not affecting the ability to perform any of the following functions: Doing all zips and buttons; washing or brushing hair; using a knife and fork together; handling small coins 2 = Symptoms, in 1 arm or both arms, affecting but not preventing any of the above-mentioned functions 3 = Symptoms, in 1 arm or both arms, preventing 1 or 2 of the above-mentioned functions 4 = Symptoms, in 1 arm or both arms, preventing 3 or all of the functions listed, but some purposeful movements still possible 5 = Inability to use either arm for any purposeful movement
Leg disability (05)	0 = Walking not affected 1 = Walking affected, but walks independently outdoors 2 = Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors 3 = Usually uses bilateral support (sticks, crutches, 2 arms) to walk outdoors 4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help 5 = Restricted to wheelchair, unable to stand and walk a few steps with help
Overall disability = Arm disability + Leg disability	

The INCAT score is a 10-point scale that covers the functionality of legs and arms. Scores for arm disability range from 0 to 5, and scores for leg disability also range from 0 to 5.

The INCAT (total) score is the sum of these 2 scores and ranges from 0 to 10.

For the “adjusted” INCAT score, changes in the function of the upper limbs from 0 (normal) to 1 (minor symptoms) or from 1 to 0 will not be recorded as deterioration or improvement, because these changes are not considered clinically significant.

11.8. Appendix 8: Medical Research Council Scale

MRC Scale[35]	
0	Complete paralysis
1	Minimal contraction
2	Active movement with gravity eliminated
3	Weak contraction against gravity
4	Active movement against gravity and resistance
5	Normal strength

The scale is bilaterally applied to 6 muscle groups of the upper and lower limbs in order to obtain a summed score ranging from 0 to 60 for the MRC scale: 1) arm abductors; 2) elbow flexors; 3) wrist extensors; 4) hip flexors; 5) knee extensors; and 6) foot dorsiflexors.

11.9. Appendix 9: Inflammatory Rasch-built Overall Disability Scale (I-RODS)

RODS for GBS – CIDP - MGUSP

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box ("x"). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If you situation fluctuates, your answer should be based on how you *usually* perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

Are you able to	Mark the best option with **"x"**		
Task	**Not possible to perform**	**Possible, but with some difficulty**	**Possible, without any difficulty**
	[0]	**[1]**	**[2]**
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14.	do the shopping?	☐	☐	☐
15.	catch an object (e.g., ball)?	☐	☐	☐
16.	bend and pick up an object?	☐	☐	☐
17.	walk one flight of stairs?	☐	☐	☐
18.	travel by public transportation?	☐	☐	☐
19.	walk and avoid obstacles?	☐	☐	☐
20.	walk outdoor < 1 km?	☐	☐	☐
21.	carry and put down a heavy object?	☐	☐	☐
22.	dance?	☐	☐	☐
23.	stand for hours?	☐	☐	☐
24.	run?	☐	☐	☐

11.10. Appendix 10: [redacted]

[redacted]

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

[redacted]

11.11. Appendix 11: Columbia-Suicide Severity Rating Scale (C-SSRS)

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 3 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation* Past X Months - ***Most Severe Ideation:*** ___ *Type # (1-5)* ___ *Description of Ideation*	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	___

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 1 Years
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Has subject engaged in Non-Suicidal Self-Injurious Behavior?		
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 2 of 2

Source: C-SSRS; Baseline/Screening Version; Version 1/14/09; Available at: https://cssrs.columbia.edu/wp-content/uploads/C-SSRS1-14-09-BaselineScreening.pdf.

11.12. Appendix 12: Possible Adaptations of Trial Protocol During COVID-19 Pandemic

Introduction

The aim of the ARGX-113-1802 trial is to investigate a new subcutaneous (SC) treatment option for patients with chronic inflammatory demyelinating polyneuropathy (CIDP). This SC treatment consists of efgartigimod with recombinant human hyaluronidase PH20 (rHuPH20) (called efgartigimod PH20 SC) and could offer clinically significant benefits to CIDP patients.

argenx has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. Following careful evaluation, the risk/benefit profile of efgartigimod use in clinical trials has not changed in the context of this pandemic. This decision was made based on efgartigimod's mechanism of action, the safety data generated to date, and provisions made in the clinical trials with efgartigimod for safety reporting and withholding treatment upon evidence of infection. This assessment will be reviewed regularly to consider new information about the pandemic and the ongoing, continuous assessment of adverse events reported during argenx clinical trials.

Based on this risk-benefit assessment, the clinical trial ARGX-113-1802 can be conducted, however, because of the pandemic argenx acknowledges that considerable difficulties for participating centers to meet all previously planned assessments might occur (see SoA in Section 1.3). Therefore, an Appendix with possible adaptations to this trial has been developed so that sites can follow this Appendix in case a patient cannot have the visit at the trial site (see below) and a visit at home or an alternative convenient location will be performed. This Appendix describes a minimum number of assessments required to guarantee the safety and well-being of the patients during the trial and to secure the collection of the critical parameters for analysis. It remains at the investigator's discretion to assess if it is in the best interest of the patient to participate/continue in the trial.

Note that a "home visit" as described in this Appendix could also be a visit at an alternative convenient location.

Note that the home nurse, who will go to the patient in case of a home visit, could also be another qualified person to perform all tasks (eg, a physician). In addition, a home nurse can be qualified personnel from an alternative convenient location if the trial visit cannot be performed at the trial site.

POSSIBLE ADAPTATIONS TO ARGX-113-1802 TRIAL PROTOCOL DURING COVID-19 PANDEMIC

Implementation of This Appendix

- Implementation for all sites includes social distancing, personal protective equipment (PPE), and a telephone call before each trial visit for checking of COVID-19 symptoms.
- The adaptations to the visits and procedures described in this Appendix that are acceptable alternatives to the main protocol procedures should only be implemented in exceptional cases and after approval of the sponsor and/or CRO. Approval will be

granted based on the possibility of the patient to go to the site and per local and/or hospital regulations.

The Appendix is intended for countries and/or sites in geographical areas where COVID-19 has affected trial sites' workload, severe movement restrictions have been imposed, or when there is a risk to patients/trial staff if attending trial sites for trial visits. The initial duration of the implementation of this Appendix will be agreed and can be extended based on the local epidemic status.

When a (home) visit is performed under this COVID-19 Appendix, it should be documented as a COVID-19 (home) visit in the eCRF for the applicable visit.

Testing for COVID-19

Additional testing for COVID-19 beyond that mandated by relevant local authorities is not required at the start of the study. However, argenx recommends patients who develop symptoms of COVID-19 during the trial to be tested.

Protecting Home Nurse and Site Staff From COVID-19

The home nurse and site staff as well as qualified personnel from an alternative convenient location. Staff should apply appropriate social distancing and use personal protection equipment according to the local hospital and governmental regulations/recommendations; see also below.

Patients With COVID-19 (Either a Positive Test or With Symptoms [Suspicion of COVID-19 Infection])

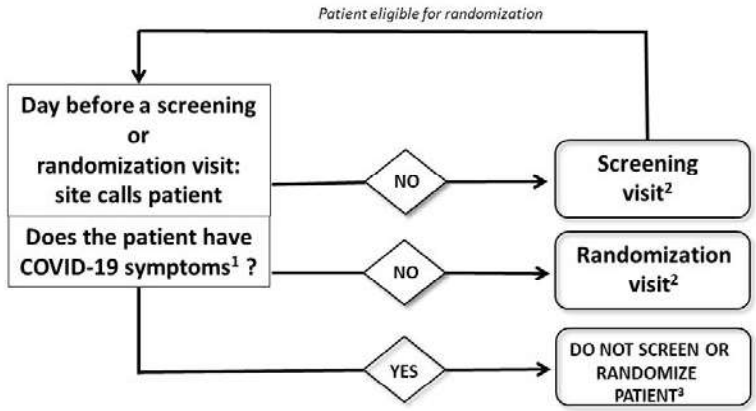
Patients with a COVID-19 infection should not enter the trial. In case a patient develops a COVID-19 infection when he/she is in the trial, the following applies.

The instructions to manage an infection that are in the main protocol are also applicable in case of an infection with COVID-19 (ie, it will be considered an AESI similar to all infections). Treatment should be interrupted until the patient is considered recovered from COVID-19 (according to the local recommendations).

During the pandemic, the trial site staff should contact patients prior to each visit to enquire about COVID-19 symptoms and exposure using the flow charts below and make a decision on proceeding or postponing the visit according to the following flow charts.

The following symptoms should be specifically addressed during that phone call: Fever, cough, sneezing, loss of taste/smell, difficulties breathing/chest tightness.

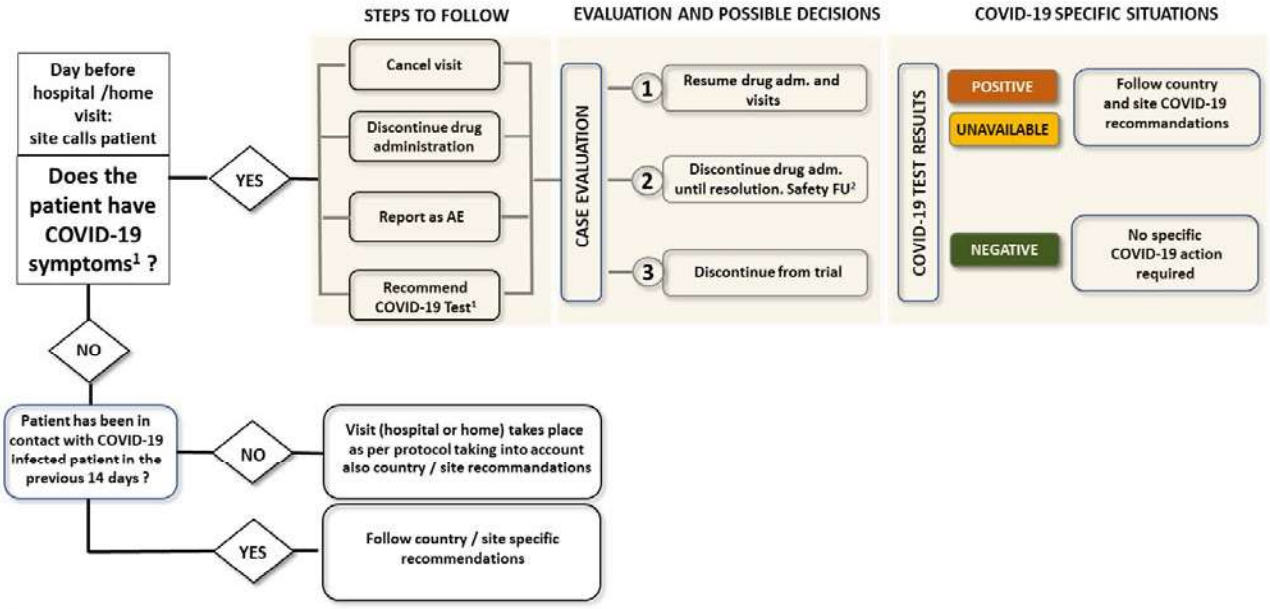
COVID-19 OUTBREAK: IMPACT ON ARGENX STUDIES – SCREENING AND RANDOMIZATION OF PATIENTS



Footnotes:

1. *No COVID-19 test for screening or randomization visits unless required/recommended by country or site.*
2. *Visit takes place as per protocol following country/site recommendation, if applicable.*
3. *Screening / randomization can be re-considered at a later time following country/site recommendation if applicable.*

COVID-19 OUTBREAK: IMPACT ON ARGENX STUDIES – PATIENTS ALREADY IN THE STUDY



[1]*Encourage and facilitate execution of COVID-19 test (PCR):* [2]*In COVID-19 positive patients, consider resuming drug administration, visits and study assessments after recovery*

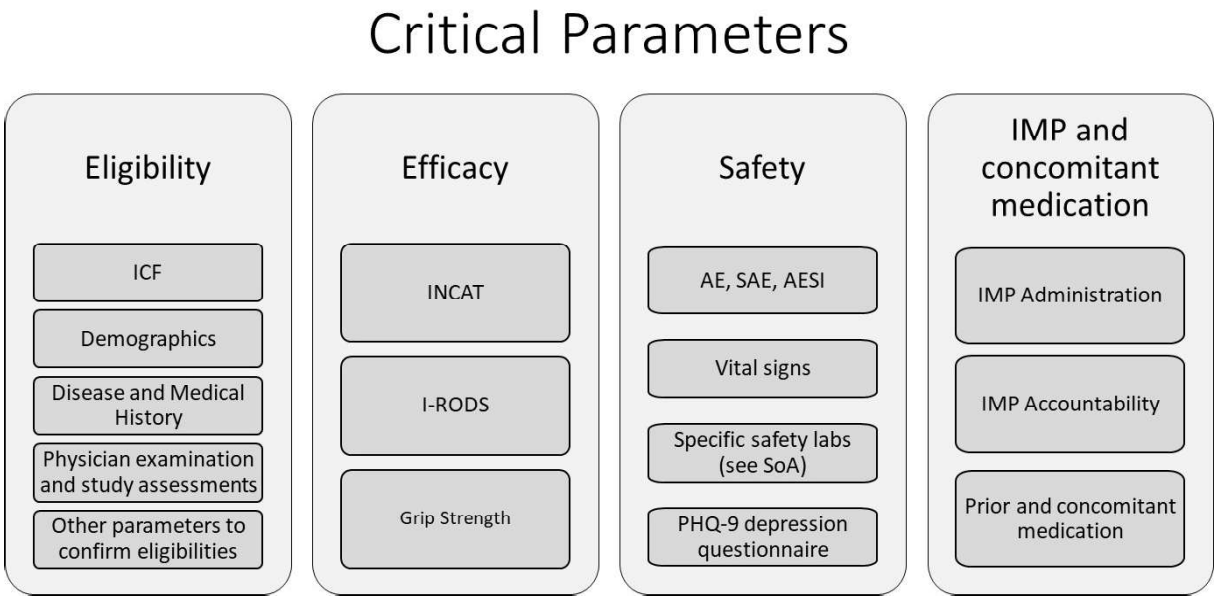
Patient with symptoms of COVID-19 infection will be treated for this infection as guided by the local health care system. Patients will be monitored by the trial site by telephone contact. In case the patient will have to be in self-isolation for a longer period than 2 weeks, it will be discussed on a case by case basis with the sponsor and/or with the CRO whether the patient can remain in the trial.

Once a patient has recovered, the patient can continue the trial and receive trial medication, provided that he/she has not received/is not receiving prohibited medication (see Section 7.4.2).

Critical Parameters to be Collected During the Trial

Please note that, if feasible, all assessments, including those that are not critical (ie, indicated as assessments that are not mandatory in the SoA in Section 11.12.1) should be performed.

The critical parameters which are mandatory to be collected during the trial, are summarized below:



During the COVID-19 pandemic, the collection of these critical parameters is specified in the SoA for both stages of the trial in Section 11.12.1 (indicated in red solid dots).

- The evaluation of eligibility for the trial will be as described in the main protocol. The screening visit must be performed at the trial site (see below).
- For the evaluation of efficacy, safety, and for the IMP administration and accountability, certain modifications compared to the main protocol are allowed in this protocol compared to the main protocol (see below).

Mandatory Site Visits and Allowed Home Visits

In order to collect the critical parameters of the trial, certain visits have to be performed at the site and other visits can be at home:*

- Screening Visit

The screening visit of the trial needs to be performed at the trial site. If it is not possible to go to the trial site due to the COVID-19 situation, the screening visit is to be postponed and has to wait until the situation changes and the patient is able to go to the trial site. Note that transportation to the trial site can be facilitated if the situation due to the COVID-19 pandemic allows this.

- Baseline Visits of Stage A and Stage B

The baseline visit of Stage A (D1A) and the baseline visit of Stage B (D1B) have to be performed at the trial site. If it is not possible to go to the trial site for these baseline visits due to the COVID-19 situation, the sponsor or CRO have to be contacted as soon as possible to discuss viable options.

- Other Trial Visits

All trial visits, other than the screening visit and the baseline visits of Stage A and Stage B that are originally planned to be site visits can be performed at home (or at an alternative convenient location) during the COVID-19 pandemic. A home nurse will travel to the patient's home to conduct this visit (or the patient will go to an alternative convenient location). The treating physician will talk to the patient via an audio or video interview to elicit AE, concomitant medications, and general well-being of the patient. The evaluating physician will perform efficacy assessments using a video interview (or via a telephone only if a video interview is not possible) with the patient. The assessments via an audio or video interview will be conducted before the home nurse administers the trial medication. The division of tasks between the treating physician, evaluating physician, and home nurse are indicated in the following scheme.

Stage B visits that were originally planned as home visits for IMP administration, remain as described in the main protocol.

* Note that a "home visit" as described in this Appendix could also be a visit at an alternative convenient location.

Scheme for Home Visits[a]		
Critical Assessments	**Performed by**	**Method of Assessment**
• ICF Addendum (not initial ICF at screening, explained to patient) • Adverse events • Concomitant medication • Confirmation that IMP can be administered	Treating Physician	Audio or video interview
• Adjusted INCAT • Grip strength	Evaluating Physician	Video interview (or via telephone if video interview is not possible)
• Bring device for efficacy assessments; including I-RODS and the patients reported outcomes questionnaire PHQ-9 • Vital signs • Blood draw • IMP administration	Home nurse	In person at patient's home[a]

a. Note that a "home visit" could also be a visit at an alternative convenient location.

Efficacy Assessments

- The 3 critical efficacy assessments of the trial are:
  - Adjusted INCAT
  - I-RODS
  - grip strength

During home visits, 2 similar devices will be used to capture these assessments. One device will remain at the site with the evaluating physician and the other device will be taken by the home nurse to the patient. The evaluating physician will perform the adjusted INCAT and grip strength assessments via video link between the 2 devices (or via a telephone only if a video interview is not possible). The home nurse will thereafter provide the other device to the patient to perform the I-RODS assessment.

- MRC Sum Score and TUG are considered non-critical variables and will not be measured at home visits.

Patient-Reported Outcomes (PROs)

- During a home visit, patient-reported outcomes (PROs) will be performed by the patient on the device provided by the home nurse.
- The PHQ-9 depression questionnaire (suicidality question) needs to be done at all scheduled visits, also if this visit is performed at the patient's home (or at an alternative convenient location).
- Other PROs are not considered as critical data and be performed only if feasible during a home visit (or during a visit at an alternative convenient location).

Safety Assessments

- Adverse event

During home visits, a telephone/video interview will be conducted by the treating physician or designee about possible AEs. Any suspected COVID-19 infection relevant signs or symptoms (including an abnormal laboratory findings) will be reported as an AE, with clear distinction whether it is a confirmed test positive COVID-19 infection or suspected infection if not tested.

- Vital signs

During home visits, vital signs (heart rate, body temperature, and blood pressure) will be measured by the home nurse at the beginning of the home visit and the results will be communicated to the treating physician. If pyrexia is detected, the home nurse should call the trial site immediately and await further instructions from the treating physician.

- Safety laboratory testing

During home visits, the home nurse will take blood samples for safety laboratory testing immediately before IMP administration. Ideally, tubes from the central laboratory will be used. However, if needed, local laboratory tubes and venipuncture equipment can be used after prior agreement with the central laboratory.

During home visits, urine samples will be taken for safety laboratory testing and for pregnancy testing (if applicable).

In case transfer of laboratory samples to the central laboratory is not available or may be prolonged, a local laboratory can be used. A certification of the local laboratory is required. Laboratory reports should be sent to and reviewed by the investigator and any abnormalities will be evaluated for clinical significance and any significant laboratory findings should be recorded as AEs. The laboratory report should be kept as a source document.

- Electrocardiogram (ECG)

At screening, Stage A visit 1 and Stage B visit 1 (which are performed at the site), ECGs are required. A local ECG machine from the site can be used in case equipment from the central ECG laboratory does not arrive at the site. A test transfer to the central ECG laboratory (eResearch Technology [ERT]) with an anonymized test ECG is required. Requirement for the test ECG and test transfer are described in the user guide (“site upload tool quick guide”) from ERT. Except for screening, an ECG is not considered as critical data at other visits and will not be done in case of a home visit.

Blood Sampling for Tests Other Than Safety Laboratory Testing

During home visits, the home nurse will draw the blood samples for laboratory parameter evaluation. Blood sampling will be performed immediately before IMP administration.

Concomitant Medication

At the time of the home visit, the site treating physician will telephone/video interview the patient about concomitant medications. It will be documented whether concomitant medication is taken for a confirmed test positive COVID-19 infection or suspected infection (if not tested).

IMP Administration

IMP can be administered at home by a qualified person (eg, home nurse) after confirmation of the treating physician.

Trial Endpoint

The criteria for the trial endpoint for a patient in Stage A or Stage B as described in the main protocol, also apply to this Appendix.

11.12.1. Schedule of Activities (SoA) During COVID-19 Pandemic

In the SoA for Stage A and Stage B of the ARGX-113-1802 trial (see below), the mandatory assessments are indicated in red solid dots. The assessments that need to be performed only if feasible during the COVID-19 pandemic are indicated in black open circles. At site visits, all assessments have to be performed (critical [red solid dots] and non-critical [black open circles]). At home visits (or a visit at an alternative convenient location): assessments can be limited to the mandatory assessments (critical [red solid dots]).

SoA for Screening, Run-in, and Stage A During COVID-19 Pandemic

	Screening[a] ≤28 days	Run-in Period ≤12 weeks[b]		Stage A: Open-label Period ≤12 Weeks (With Optional 1 Additional Week)[c]														Unsche-duled[e]	Safety Follow-up[f]
		RI-V1	RI-V2 to RI-V4	A-V1	A-V2	A-V3	A-V4	A-V5	A-V6[c]	A-V7[c]	A-V8[c]	A-V9[c]	A-V10[c]	A-V11[c]	A-V12[c]	A-V13[c] (Addi-tional)	EOSA/ ED[d]	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D8	D15	D22	D29	D36[c]	D43[c]	D50[c]	D57[c]	D64[c]	D71[c]	D78[c]	D85			
Assessment/Procedure		±0 days	±2 days	±0 days	±2 days														
Informed consent	●																		
Demographics	●																		
In-/exclusion criteria	●	O		●															
Medical history[g]	●																		
12-lead ECGs	●			●													O	O	O
CDAS	●																		
Physical exams	●[h]	O	O	●	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Vital signs[i]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	O	●
Pregnancy test	●[j]	●[k]	●[k]	●[k]				●[k]				●[k]					●[k]	O[k]	●[k]
Adjusted INCAT score		●	●	●	●	●	●	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	(●)[l]	●	●	O	
MRC sum score		O	O	●	O	O	O	O	(O)[l]	O	(O)[l]	O	(O)[l]	O	(O)[l]	O	O	O	
I-RODS score		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	O	

	Screening[a] ≤28 days	Run-in Period ≤12 weeks[b]		Stage A: Open-label Period ≤12 Weeks (With Optional 1 Additional Week)[c]														Unsche-duled[e]	Safety Follow-up[f]
		RI-V1	RI-V2 to RI-V4	A-V1	A-V2	A-V3	A-V4	A-V5	A-V6[c]	A-V7[c]	A-V8[c]	A-V9[c]	A-V10[c]	A-V11[c]	A-V12[c]	A-V13[c] (Addi-tional)	EOSA/ ED[d]	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D8	D15	D22	D29	D36[c]	D43[c]	D50[c]	D57[c]	D64[c]	D71[c]	D78[c]	D85			
Assessment/Procedure		±0 days	±2 days	±0 days	±2 days														
Mean grip strength		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	O	
TUG test		O	O	●	O	O	O	O	O	O	O	O	O	O	O	O	O	O	
EQ-5D-5L				●													O	O	
[redacted]				●													O	O	
[redacted]		O[m]															O	O	
[redacted]				●													O	O	
[redacted]				●													O	O	
[redacted]					O												O	O	
Suicidality assessment[n]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	O	●
Blood & urine clinical laboratory safety tests	●[o]			●	O	●	O	●									O	O	●
HIV, HBV, HCV, and tuberculosis testing	●																	O[p]	
Blood sampling for PK and PD analysis[q]				●[x]	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Blood sampling for immunogenicity analysis[r]	●[x]			●[x]		O		O				O					O	O	O
[redacted]		O[x]		●[x]													O	O	

	Screening[a] ≤28 days	Run-in Period ≤12 weeks[b]		Stage A: Open-label Period ≤12 Weeks (With Optional 1 Additional Week)[c]													Unsche-duled[e]	Safety Follow-up[f]
		RI-V1	RI-V2 to RI-V4	A-V1	A-V2	A-V3	A-V4	A-V5	A-V6[c]	A-V7[c]	A-V8[c]	A-V9[c]	A-V10[c]	A-V11[c]	A-V12[c]	A-V13[c] (Addi-tional)	EOSA/ ED[d]	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D8	D15	D22	D29	D36[c]	D43[c]	D50[c]	D57[c]	D64[c]	D71[c]	D78[c]	D85			
Assessment/Procedure		±0 days	±2 days	±0 days	±2 days														
IMP self-administration training[t]				●	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]	O[t]			
IMP administration (SC)[u]				●[u]	●	●	●	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]	●[u]			
IMP accountability[v]				●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Adverse events[w]	‹----------●---------›																		
Concomitant therapies[g,w]	‹----------●---------›																		

Footnotes are on next page

ADA=anti-drug antibodies; AE=adverse event; [redacted] CDAS=CIDP disease activity status; CIDP=chronic inflammatory demyelinating polyneuropathy; D1A=baseline of Stage A; D1B=baseline of Stage B; ECG=electrocardiogram; ECI=evidence of clinical improvement; ECMD=evidence of clinically meaningful deterioration; ED=early discontinuation; EOSA=end of Stage A; EQ-5D-5L=EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire; [redacted]; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=informed consent form; IgG=immunoglobulin G; IMP=investigational medical product; INCAT=inflammatory neuropathy cause and treatment; I-RODS=Inflammatory-Rasch-built Overall Disability Scale; OLE=open-label extension; PD=pharmacodynamic(s); [redacted] PK=pharmacokinetic(s); rHuPH20=recombinant human hyaluronidase PH20; [redacted]; MRC=Medical Research Council; SAE=serious adverse event; SC=subcutaneous(ly); [redacted]; TUG=timed up and go; Unsch=unscheduled; V=visit; W=week.

a. Within 28 days before the first day of run-in (visit RI-1). If needed a medical monitor can authorize the extension of the screening period. For treatment-naïve patients screening can occur within 28 days before D1A, if during screening documented evidence for worsening on the adjusted INCAT score within 3 months prior to screening is available compared to previous adjusted INCAT score within 6 months prior to screening.

b. Site/home visit every 4 weeks. R1-V1: day 1 of run-in; R1-V2:run-in week 4 (±2 days); R1-V3: run-in week 8 (±2 days), and R1-V4: run-in week 12 (±2 days). A patient showing ECMD will enter Stage A immediately. Patients will receive appropriate training and instructions to assess every week the disability status by means of I-RODS and grip strength. If the patient does not have evidence of ECMD by the end of the run-in period, then he/she should be recorded as a run-in failure.

c. Weekly administration of efgartigimod PH20 SC (±2 days). Patients, who show ECI only after the 12th IMP administration (ie, 1 week after the A-V12 visit), may be allowed to extend Stage A for a further week with an additional visit (the visit at which ECI is observed for the first time will then be A-V13) and patients will need to come back 1 week later (ie, 1 week after A-V13) to confirm ECI.
All patients with confirmed ECI following a minimum of 4 IMP administrations will have an EOSA visit and will enter Stage B. If the patient does not show confirmed ECI during Stage A, then he/she will have an EOSA visit and end the trial after a follow-up visit 28 days after the last administration of IMP.

d. The assessments in this visit are for patients who end Stage A (ie, EOSA visit; for patients with or without confirmed ECI) as well as for patients who discontinue the trial prematurely (ie, ED visit). Patients with confirmed ECI can continue the trial in Stage B (in this case, the patients will have a combination of the EOSA visit and the Baseline Stage B [D1B] visit).

Note: Patients who end Stage A with confirmed ECI and will go to Stage B, should have had at least 4 IMP administrations during Stage A.
Note: Patients with ECI only after 12 IMP administrations in Stage A, may be allowed to extend Stage A for 1 more week (in order to determine if ECI is confirmed or not) with an additional consecutive visit (see footnote above).
Note: Patients with ECI preferably have a combined visit that includes the last visit of Stage A (EOSA) and the first visit of Stage B (D1B). In this case, all assessments at EOSA are mandatory.

e. The investigator can decide which of the assessments need to be performed at each unscheduled visit (refer to Section 5.1.5).

f. Only applicable for patients who do not continue in Stage B and for patients who prematurely discontinued IMP in case IMP was stopped less than 28 days before the last trial visit.

g. At screening, all available vaccination history will be captured as part of prior medication. For vaccines where multiple doses or boosters are received, only the most recent one must be recorded. Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.
Note: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.

h. Includes physical examination, height, and weight.

i. Includes semi-supine blood pressure and heart rate, and body temperature.

j. A serum pregnancy test will be conducted at screening.

k. Urine pregnancy tests will be conducted every 4 weeks during the trial and at the follow-up visit.

l. These tests are only required for confirmation of improvement (for patients with improvement in the previous visit).

[redacted]

n. At screening, suicidality will be assessed with the Columbia-suicide severity rating scale (C-SSRS) (see Section 9.2). During the trial, suicidality will be assessed by specifically answering 1 question from the PHQ-9 depression questionnaire (see Section 9.15).

o. At screening, total IgG will be measured (by central laboratory as part of the blood chemistry tests) to determine eligibility.

p. Serology can be retested only during the screening period.

q. For PK, pre-dose (within 2 hours prior to start of IMP administration at the trial visits) samples will be taken. At these time points, blood samples will also be taken for PD analysis. PD analysis includes the measurement of total IgG. IgG testing must not be performed locally.

r. Blood samples for immunogenicity testing will be taken pre-dose at the trial visits to measure ADA against efgartigimod (measured in serum) and antibodies against rHuPH20 (measured in plasma).

s. Optional blood samples will be taken for autoantibodies testing (serum) and serum-sample storage for future testing.

t. Patients will be trained to self-administer IMP at the site (foreseen in the OLE trial; not in the ARGX-113-1802 trial) during the first 4 visits when IMP is administered; thereafter, training for self-administration is optional (only if needed).

u. IMP will be administered weekly at the site/home in Stage A (IMP administration will be after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses and after all assessments needed for determination of ECI). The first IMP administration in Stage A can be within 24 hours after observing ECMD during the run-in period. Patients will receive a minimum of 4 IMP administrations in Stage A. Note that IMP in Stage A will **not** be administered if ECI is confirmed at the visit (and the patient has received at least 4 IMP administrations). When ECI is confirmed (ie, ECI observed at the second consecutive visit), the patient will be randomized and receive the first double-blind IMP administration in Stage B (ie, the visit at which ECI is confirmed will be a combination of the EOSA visit and the Stage B baseline [D1B] visit).

v. IMP kits will be returned to the site where IMP accountability will be performed when the kits are available, preferably every 4 weeks.

w. AEs and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity. In case of early discontinuation, any AEs/SAEs should be assessed for 30 days following the ED visit or until satisfactory resolution or stabilization.

x. Blood samples may also be used to cross-validate the PK, PD, biomarker, and ADA assays in CIDP matrix (serum and plasma).

SoA for Stage B and Follow-up During COVID-19 Pandemic

	Stage B: Randomized-withdrawal Treatment ≤48 weeks													Un-scheduled	Safety Follow-up[d]
	B-V1	B-V2	B-V3	B-V4	B-V5	B-V6	B-V7	B-V8	B-V9	B-V10	B-V11	B-V12	B-V13	UnschV[c]	28 (±3) days after last IMP dose
	D1B[a]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ED[b]		
Assessment/Procedure	±0 days	±2 days													
Randomization	●														
12-lead ECGs	●			o			o			o			o	o	o
Physical exam[e]	●	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Vital signs[f]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Pregnancy test[g]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Adjusted INCAT score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
MRC Sum score	●	o	o	o	o	o	o	o	o	o	o	o	o	o	
I-RODS score	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
Mean grip strength	●	●	●	●	●	●	●	●	●	●	●	●	●	●	
TUG test	●	o	o	o	o	o	o	o	o	o	o	o	o	o	
EQ-5D-5L	●			o			o			o			o	o	
[redacted]	●			o			o			o			o	o	
[redacted]	●			o			o			o			o	o	
[redacted]	●			o			o			o			o	o	
[redacted]	●			o			o			o			o	o	
[redacted]													o	o	
Suicidality assessment	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood & urine safety tests	●			●			●			●			●	o	●
Blood sampling for PK and PD analysis[h]	●	o	o	o	o	o	o	o	o	o	o	o	o	o	o

	Stage B: Randomized-withdrawal Treatment ≤48 weeks													Un-scheduled	Safety Follow-up[d]
	B-V1	B-V2	B-V3	B-V4	B-V5	B-V6	B-V7	B-V8	B-V9	B-V10	B-V11	B-V12	B-V13	UnschV[c]	28 (±3) days after last IMP dose
	D1B[a]	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48/ED[b]		
Assessment/Procedure	±0 days	±2 days													
Blood sampling for immunogenicity analysis[i]	●	o	o	o	o	o	o	o	o	o	o	o	o	o	o
[redacted]	●			o			o			o			o	o	
IMP self-administration training[k]	●	o	o	o	o	o	o	o	o	o	o	o			
IMP administration (SC)[l]	●	●	●	●	●	●	●	●	●	●	●	●[l]			
IMP dispensation	●	●	●	●	●	●	●	●	●	●	●	●[l]			
IMP accountability[m]	●	●	●	●	●	●	●	●	●	●	●	●	●		
Adverse events[n]	‹----------●												----------›		
Concomitant therapies[n,o]	‹----------●												----------›		

Footnotes are on next page

ADA = anti-drug antibody; AE = adverse event; [redacted] D1B = baseline of Stage B; ECG = electrocardiogram; ECI = evidence of clinical improvement; ED = early discontinuation; EQ-5D-5L = EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire; [redacted] Scale; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IgG = immunoglobulin G; IMP = investigational medical product; INCAT = inflammatory neuropathy cause and treatment; I-RODS = Inflammatory-Rasch-built Overall Disability Scale; OLE = open-label extension; PD = pharmacodynamic(s); [redacted]; PK = pharmacokinetic(s); rHuPH20 = recombinant human hyaluronidase PH20; [redacted]; MRC = Medical Research Council; SAE = serious adverse event; SC = subcutaneous(ly); [redacted] TUG = Timed up-and-go; Unsch = unscheduled; V = visit; W = week.

a. D1B will occur at the same visit, at which ECI has been confirmed in Stage A. There is no need to schedule an additional visit for D1B. All assessments are performed prior to IMP administration.

b. The assessments in this visit are for patients who end Stage B as well as for patients who discontinue the trial prematurely (ie, ED visit). Patients who will roll over to the OLE trial, will have a combination of this last visit in the ARGX-113-1802 trial and the first visit of the OLE trial ARGX-113-1902. In this case, all assessments at this visit are mandatory, [redacted] which should only be assessed if feasible.

c. The investigator can decide which of the indicated assessments need to be performed at each unscheduled visit (refer to Section 5.1.5).

d. This visit is not applicable for patients who roll over to the OLE trial and for patients who prematurely discontinued IMP in case IMP was stopped less than 28 days before the last trial visit.

e. Includes physical examination and weight.

f. Includes semi-supine blood pressure and heart rate, and body temperature.

g. Urine pregnancy test every 4 weeks and at the follow-up visit.

h. For PK, pre-dose (within 2 hours prior to start of IMP administration at the trial visits) samples will be taken. At these time points, blood samples will also be taken for PD analysis. PD analysis includes the measurement of total IgG. IgG testing must not be performed locally.

i. Blood samples for immunogenicity testing will be taken pre-dose at the trial visits to measure ADA against efgartigimod (measured in serum) and antibodies against rHuPH20 (measured in plasma).

j. Optional blood samples will be taken for autoantibodies testing (serum) and serum-sample storage for future testing.

k. Patients will be trained (refreshment training), if needed, to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1802 trial).

l. The first IMP administration in Stage B can be within 24 hours after confirmation of ECI in Stage A. IMP will be administered at the site/home at the scheduled visits. This will be after blood samples have been taken for laboratory safety, PK, PD, immunogenicity, and/or biomarker analyses. For IMP administrations between the scheduled visits, the patient can choose between nurse home visits or return to the trial site for the SC injection only. The last planned IMP administration is at Week 47.

m. IMP kits will be returned to the site where IMP accountability will be performed when the kits are available, preferably every 4 weeks.

n. AEs and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity. In case of early discontinuation, any AEs/SAEs should be assessed for 30 days following the ED visit or until satisfactory resolution or stabilization.

o. Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.
   Note: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.

11.13. Appendix 13: Protocol Amendment History

General Amendment 3, General Protocol Version 4.0:

The major changes from Protocol Version 3.0 compared to Protocol Version 4.0 are summarized in the table below. Deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text. Minor administrative editorial changes (eg, to improve readability or correct spelling mistakes) are not summarized in the following table:

Summary of Changes Between Protocol Version 3.0 and Protocol Version 4.0

Section(s)	Change	Rationale
• Front page	• Serious Adverse Events Reporting: **Parexel International** **8 Federal Street, Billerica, MA 01821, United States of America** ~~SGS Belgium NV, Life Sciences Division, Noorderlaan 87, 2080 Antwerp, Belgium~~ • For drug safety reporting, contact the following email address: Safety Mailbox/Fax: Email: **248700ADR@parexel.com** ~~be.life.saefax-ma@sgs.com~~ Fax: **+1 833 644-0806** ~~+32 (0)15 29 93 94~~	Updated contact information for SAE reporting.
• Synopsis, Section 6.1	• Inclusion criterion: 5. An INCAT score ≥2~~, with a score of 2 exclusively from leg disability,~~ at the first run-in visit (RI-V1; for patients entering run-in) or Stage A baseline (A-V1; for treatment-naïve patients with documented evidence for worsening on the total adjusted INCAT disability score within 3 months prior to screening). **Patients with an INCAT score of 2 at trial entry must have this score exclusively from the leg disability score; for patients with an INCAT score of ≥3 at trial entry, there are no specific requirements for arm or leg scores.**	Clarification of inclusion criterion based on an INCAT score of 2 or higher.
• Synopsis, Section 6.1	• Inclusion criterion: 6. Fulfilling any of the following treatment conditions: • Currently **(ie, within the last 6 months)** treated with pulsed corticosteroids, oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg~~, if this treatment has been started within the last 5 years before screening~~, and the patient is willing to discontinue this treatment at the first run-in visit (RI-V1); OR …	Clarification of what we mean with currently treated and adapted further, because patients treated with IVIg or SCIg for more than 5 years before screening could also benefit from treatment with efgartigimod PH20 SC.
• Synopsis, Section 6.1, Section 11.3	• Inclusion criteria: 8. Women of childbearing potential must use a highly effective **or acceptable** method of contraception ~~(failure rate of less than 1% per year)~~ from screening to 90 days after the last administration of IMP 9**a**. **Male patients agree not to donate sperm during the trial period and 90 days thereafter.** ~~Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom and his partner must use a highly effective method of contraception (failure rate of less than 1% per year) from screening to 90 days after the last administration~~	Reproductive toxicity studies with efgartigimod IV have been completed in rats and rabbits. Efgartigimod did not show a teratogenic effect (rats and rabbits), nor did it adversely affect male and female fertility or any other reproductive and developmental performance (rats). Therefore, acceptable methods of contraception can

Section(s)	Change	Rationale
	~~of IMP. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual life style of the participant) can be included. Sterilized male patients who have had vasectomy with documented aspermia post-procedure can be included. In addition, male patients are not allowed to donate sperm from screening to 90 days after the last administration of IMP.~~ • Section 11.3 "Appendix 3: Contraceptive **and Barrier** Guidance": **11.3.1. General Instructions and Definitions** **Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception.** **Male patients are not allowed to donate sperm during the period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP (trial medication injection).** **Women of childbearing potential must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before IMP can be administered.** **A woman is considered of childbearing potential unless she is either:** • **Postmenopausal, 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.** • **Surgically sterilized: Women who have had a documented permanent sterilization procedure (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).** **11.3.2. Female Contraception for Women of Childbearing Potential** **Women of childbearing potential should use a highly effective or acceptable method of contraception during the trial and for 90 days after the last administration of the IMP.** **The following highly effective and/or acceptable methods of contraception, described in the Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials[8], are allowed in this trial:** • **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:** – **Oral** – **Intravaginal**	be used in addition to highly effective methods.

Section(s)	Change	Rationale
	– **Transdermal** • **Progesterone-only hormonal contraception associated with inhibition of ovulation:** – **Oral** – **Injectable** – **Implantable** • **Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action** • **Intrauterine device (IUD)** • **Intrauterine hormone-releasing system (IUS)** • **Bilateral tubal occlusion** • **Vasectomized partner** • **Sexual abstinence** • **Male or female condom with or without spermicide** • **Cap, diaphragm, or sponge with spermicide** **11.3.3. Male Contraception** **An acceptable method of contraception is a condom.** ~~1. Women of childbearing potential must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before trial medication (injection) can be administered. Women are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle stimulating hormone (FSH) of >40 IU/L or are surgically sterilized (ie, women who had a hysterectomy, both ovaries surgically removed, or have a documented permanent female sterilization procedure including tubal ligation). FSH can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy. For patients on hormonal replacement therapy, a historical FSH value that was measured prior to initiation of hormonal replacement therapy is acceptable to determine postmenopausal status.~~ ~~2. Women of childbearing potential should use a highly effective method of contraception (ie, pregnancy rate of less than 1% per year) during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month, of:~~ ~~• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:~~ ~~o oral~~ ~~o intravaginal~~ ~~o transdermal~~ ~~• progestogen only hormonal contraception associated with inhibition of ovulation:~~ ~~o oral~~ ~~o injectable~~ ~~o implantable~~	

Section(s)	Change	Rationale
	~~• intrauterine device (IUD)~~ ~~• intrauterine hormone-releasing system~~ ~~• bilateral tubal occlusion~~ ~~• vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and documented aspermia post-procedure)~~ ~~• continuous abstinence from heterosexual sexual contact. Sexual abstinence is only allowable if it is the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.~~ ~~3. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use effective double contraception, being a condom for male patients and a highly effective form of contraception for the female partner of childbearing potential (same as for female patients described above). Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. Sterilized male patients who have had vasectomy with documented aspermia post-procedure can be included. In addition, male patients are not allowed to donate sperm during this period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP.~~	
• Synopsis	• **Maximum duration of patient involvement in the trial:** … Follow-up period for patients not rolling over into the extension trial or for patients who prematurely discontinue IMP, will be 28 days after ~~last visit or~~ **the** last dose of IMP.	Correction that the follow-up period is 28 days after the last IMP dose (and not after the last visit).
• Footnotes from Schedule of Activities in Section 1.3.1 and Section 11.11.1	• Schedule of Activities for screening, run-in, and Stage A: Footnote to "[redacted]" at first run-in visit (normal and during COVID-19 Pandemic): [redacted]	Clarification of completion of [redacted] at the first visit of the run-in period.
• Section 1.3, Section 7.4, Section 9.1.1, Section 11.2, Section 11.11.1	• Section 1.3 and Section 11.11.1 "Schedule of Activities for Screening, Run-in, and Stage A" (normal and during COVID-19 Pandemic): Addition of the following footnote to "Medical history" and "Concomitant therapies": **At screening, all available vaccination history will be captured as part of prior medication. For vaccines where multiple doses or boosters are received, only the most recent one must be recorded. Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.** ***Note*: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.**	Addition of collection of vaccination history and - for those who consent - optional measurement of antibody titers.

Section(s)	Change	Rationale
	• Section 1.3 and Section 11.11.1 "Schedule of Activities for Stage B and Follow-up" (normal and during COVID-19 Pandemic): Addition of the following footnote to "Concomitant therapies": **Any vaccination received during the trial (from screening onwards) will be entered as concomitant medication.** ***Note*: For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial.** • Section 7.4 "Prior Treatments and Concomitant Medications": … **As part of prior medication, details collected at screening should include all information the patient, his/her legally authorized representative (according to local regulations), or caregiver can remember about previous vaccinations received, including administration date and brand name, if known (note: if in the past a same vaccine was received more than once, including as booster, only the last one is to be collected). Any vaccination received during the trial, including administration date and brand name, will be entered as concomitant medication.** • Section 9.1.1 "**Vaccination History and Vaccinations During the Trial**" **At screening, the investigator will ask the patient about all vaccination received in the past. Any vaccination information the patient, his/her legally authorized representative (according to local regulations), or caregiver can remember should be recorded in the eCRF (with the brand name of the vaccine and date of vaccine administration recorded, if possible). If in the past a same vaccine was received more than once, including as booster, only the last one is to be collected. Any vaccination received during the trial, including administration date and brand name, will be entered as concomitant medication (see Section 7.4).** **For patients who provide separate consent, the titers of produced vaccination antibodies will be measured using retained blood samples (left over blood samples taken for other tests) during the trial (see Section 11.2).** • Section 11.2 "Appendix 2: Clinical Laboratory Tests": … # Blood samples may also be used to cross-validate the PK, PD, biomarker and ADA assays in CIDP matrix (serum and plasma), **as well as used for vaccination antibody testing**.	
• Section 2.2	Section 2.2 "Definition of Terms" • Definition of ECI: … Patients who have no change in adjusted INCAT score during the run-in period **and deteriorated on I-RODS**	Clarification of ECI, based on I-RODS and grip strength.

Section(s)	Change	Rationale
	and/or grip strength during run-in can be entered in Stage B in the following cases: …	
• Section 3.3.1, Section 3.3.2	• Section 3.3.1 "Benefit" … **In addition, Phase 3 studies with efgartigimod IV in patients with gMG showed that the trial's primary endpoint was met with statistical significance. The primary endpoint was defined as the "percentage of anti-acetylcholine receptor antibody (AChR-Ab) seropositive patients who, during the first cycle, have a reduction of ≥2 points in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score compared to study entry baseline for ≥4 consecutive weeks, with the first reduction occurring no later than 1 week after the last investigational medicinal product (IMP) infusion." A total of 67.7% of AChR-Ab positive patients treated with efgartigimod achieved the primary endpoint compared with 29.7% on placebo (p<0.0001). In the overall patient population (AChR-Ab seropositive and seronegative patients), 67.9% of the patients treated with efgartigimod were MG-ADL responders compared with 37.3% on placebo (p<0.0001). Other key secondary endpoints for this study were also met with high statistically significance.** • **Section 3.3.2 "Risks":** … In clinical trials to date, efgartigimod has been well-tolerated in healthy adult subjects and patients with gMG and ITP~~, separately~~**; efgartigimod was administered either IV or SC**: the majority of treatment-emergent adverse events (TEAEs) were considered to be mild (grade 1) **or moderate (grade 2)** in severity. ~~No TEAEs of grade ≥3 have been reported. The most common TEAE suspected to be related to efgartigimod is headache; however, there is no evidence that headache occurs more frequently in patients administered efgartigimod than in patients administered placebo.~~ **In the Phase 3 trials in patients with gMG, the majority of TEAEs were reported as mild (grade 1) or moderate (grade 2) in severity. The most frequently (≥5%) reported TEAEs during all cycles of efgartigimod 10 mg/kg treatment in the overall population who received at least 1 dose of efgartigimod were headache, nasopharyngitis, upper respiratory tract infection, diarrhea, urinary tract infection, nausea, myalgia, and oropharyngeal pain. TEAEs of severity of grade ≥3 that occurred in >2 patients who received efgartigimod were headache and myasthenia gravis. The only TEAE that led to efgartigimod discontinuation reported in >2 patients was myasthenia gravis. No SAEs were assessed by the investigator as related to efgartigimod treatment.**	Sections updated to align with the current version of the Investigator's Brochure (version 9.0).

Section(s)	Change	Rationale
	Four fatal cases have been reported, however, none of the fatal events were assessed by the investigator as related to efgartigimod treatment. Causes of death was unknown in a patient who died at home without witness. The other 3 patients died due to myasthenia gravis crisis, lung cancer Stage IV, and acute myocardial infarction. These 4 patients were between 55 and 79 years old and all had clear comorbidities, including underlying gMG. **Adverse drug reactions were identified based on safety data from the Phase 3 double-blind, placebo-controlled trial in patients with gMG and include upper respiratory tract infection, urinary tract infection, bronchitis, myalgia, and procedural headache. Most AESIs were mild or moderate in severity. Few patients had severe or serious AESIs reported, and no SAEs of AESIs were assessed by the investigator as related to efgartigimod treatment.** **Due to the efgartigimod mechanism of action of reducing IgG levels, AEs in the Infections and Infestations SOC have been defined as AESIs. In the Phase 3 trials with efgartigimod IV in patients with gMG, the most frequently reported treatment-emergent AESIs by PT were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and bronchitis.** ~~Injection or catheter site reactions are AEs for which there exists a reasonable possibility of a causal relationship with the efgartigimod administration procedure, although there is no evidence that these AEs are related to efgartigimod itself. Chills were reported in healthy subjects administered efgartigimod IV 25 mg/kg. However, infusion-related reactions (IRRs) are reactions that are unpredictable, non-dose related, generally unrelated to the drug's pharmacological activity, and usually resolve when treatment is discontinued. IRRs include hypersensitivity reactions and cytokine release syndromes. These reactions can occur during the infusion of a cytotoxic or monoclonal antibody therapy (uniphasic reaction) and/or within hours of an infusion (biphasic/delayed reaction) and may be caused by the therapeutic agent, diluent, or delivery vehicle. IRR symptoms, caused by the release of cytokines from the cells, include nausea, headache, tachycardia, hypotension, rash, flushing, dyspnea, bronchospasm, back pain, fever, urticaria, and edema.~~ **All therapeutic proteins have the potential to elicit immune responses, potentially resulting in hypersensitivity or allergic reactions. As with any IV injection, the potential exists for infusion-related reactions (IRRs) to occur during or within 48 hours following the administration of efgartigimod. Overall, the frequency of IRRs in the clinical trials was low. At the preferred term (PT) level, no TEAEs of drug hypersensitivity or anaphylactic reaction were reported. None of the IRRs reported**	

Section(s)	Change	Rationale
	were serious. Most IRRs were mild in severity and no IRRs resulted in a change in efgartigimod administration. ~~Because these reactions are difficult to evaluate in prospective randomized clinical trials and due to the unexpected nature of these events, patients infused IV with efgartigimod are proactively monitored at the site, based on the patient's clinical status, for at least 1 hour following the end of the infusion.~~ For administration of efgartigimod PH20 SC, the local injection site will be monitored during the trial. **In the Phase 3 trial with efgartigimod IV in patients with gMG, no differences or imbalances were observed between the efgartigimod and placebo groups in the incidence or rates of abnormal values in clinical laboratory parameters. There was no reduction in levels of serum albumin with the administration of efgartigimod. In the extension trial in patients with gMG, the most frequently reported grade ≥3 abnormalities were lymphocyte count decreased.** ~~There has been no evidence of an increased risk of infection.~~ No clinically significant changes in vital signs and/or electrocardiogram (ECG) findings have been observed in clinical trials to date. ~~No deaths have occurred in any efgartigimod clinical trial.~~	
• Section 5.4	• Section 5.4 "Measures to Minimize Bias: Randomization and Blinding" … **Refer to Section 7.2 for the preparation and administration of the IMP, thereby keeping the blind during Stage B.** …	Reference added to section with explanation how blind of IMP is kept for Stage B.
• Section 7.1	• Section 7.1 "IMP(s) Administered" … IMP will be provided by the sponsor **and is manufactured in accordance with Good Manufacturing Practice regulations**. The efgartigimod PH20 SC formulation will be provided in a vial at a concentration of 165 mg/mL **or 180 mg/mL (new concentration)** for efgartigimod and 2000 U/mL for rHuPH20 (also referred to as ARGX-113/rHuPH20). Each dose of efgartigimod PH20 SC will include 1000 mg efgartigimod. **Note that there will be a transition period during which both formulations of efgartigimod PH20 SC (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL) will be used. After this transition period, all patients will receive the efgartigimod PH20 SC formulation with efgartigimod at the higher concentration of 180 mg/mL. The formulation with the higher concentration of efgartigimod (180 mg/mL) reduces the dosing volume for each SC injection.** Placebo will be vehicle (with 2000 U/mL of rHuPH20) provided in a vial as ready SC formulation. **For both**	Efgartigimod PH20 SC will be used with efgartigimod at a higher concentration (180 mg/mL instead of 165 mg/mL), thereby reducing the dosing volume for each SC injection. The only difference between the 165 mg/mL and 180 mg/mL batches is a higher protein concentration (±10% higher protein concentration with 180 mg/mL compared to 165 mg/mL) and a slight reduction of the dosed amount of rHuPH20 with the new formulation. This difference is not expected to result in a different activity or safety profile.

Section(s)	Change	Rationale
	efgartigimod PH20 SC formulations (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL), a corresponding placebo is available containing placebo drug product at the same volume and in the same vial as the active drug product.	
• Section 7.2	• Section 7.2 "Preparation, Handling, Storage, Administration, and Accountability" ~~…~~ ~~For Stage B IMP will be provided in a blinded vial. The trained and authorized site staff will blind the syringe for administration using a yellow blinding foil covering the barrel of the syringe before withdrawing IMP from the blinded vial. The administration is then performed by the site staff who prepared the syringe.~~ **Efgartigimod PH20 SC will be provided as a sterile, clear to opalescent, yellowish solution for SC injection.** **Placebo will be provided as a sterile, colorless, clear solution for injection in glass vials with the same formulation as the efgartigimod PH20 SC solution for injection, but without the active ingredient.** **The vials for the double-blind Stage B will be covered with a blinding shell.** **The trained and authorized staff will use an amber colored syringe for preparation and administration of IMP. The administration is then performed by the site staff who prepared the syringe.**	Clarification of IMP presentation, preparation, administration, and blinding methods.
• Section 9.4.1, Section 10.1.5.1	• Section 9.4.1 "Adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score": … **There are 3 different baseline INCAT scores during the trial, at the beginning of each stage. Each baseline INCAT score is always the total INCAT score (not the adjusted INCAT score, which is used for post-baseline assessments):** • **Baseline run-in period = Total INCAT score at the first visit of the run-in period (RI-V1)** • **Baseline Stage A = Total INCAT score at D1A (ie, the first visit of Stage A [A-V1])** • **Baseline Stage B = Total INCAT score at D1B (ie, the first visit of Stage B [B-V1])** ***Note*: The baseline total INCAT score is calculated as the sum of the arm and leg sub score, without adjustment of the arm sub score.** **For the post-baseline visits, the adjusted INCAT score calculation is based on the baseline of the corresponding stage.** • Section 10.1.5.1. "Trial Baselines" • **The baseline value for the run-in period will be the assessment recorded at visit R1-V1.** The baseline value	Clarification of INCAT baseline.

Section(s)	Change	Rationale
	for Stage A will be the last assessment prior to the first dose of open-label trial medication in Stage A. …	
• Section 11.4	Section 11.4 "Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting." • Section 11.4.1 "Definition of AE": AE Definition: An AE is any untoward medical occurrence in a ~~patient or~~ clinical trial patient, … **Definition of Unsolicited and Solicited AE:** **An unsolicited AE is an AE that was not solicited using a Patient Diary and that is communicated by a patient who has signed the informed consent (or was signed by the patient's legally authorized representative [according to local regulations]). Unsolicited AEs include serious and non-serious AEs.** **Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The patient will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of patient's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the patient's records.** **Unsolicited AEs that are not medically attended nor perceived as a concern by the patient will be collected during interview with the patient and by review of available medical records at the next visit.** **Solicited AEs are predefined local (at the injection site) and systemic events for which the patient is specifically questioned, and which are noted by the patient in his/her diary.** **Events to be collected as AEs ~~Meeting the AE Definition~~** … **Events NOT to be collected as AEs ~~Meeting the AE Definition~~** … • Section 11.4.2 "Definition of SAE": **An SAE is defined as any untoward medical occurrence that, at any dose:** c. **Requires inpatient hospitalization or prolongation of existing hospitalization** … Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious**ness** criteria, the event ~~is~~ **will be considered as** serious. … Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not ~~considered~~ **collected as** an AE.	Appendix for AEs/SAEs updated to align with the current protocol template of argenx, including addition of causality assessment and clarification of SAE reporting.

Section(s)	Change	Rationale
	• Section 11.4.3 "Recording and Follow-up of AE and/or of SAE AE and SAE Recording: … It is not acceptable for the investigator to send photocopies of the patient's medical records to **the SAE coordinator/sponsor** ~~SGS~~ in lieu of completion of the AE/SAE CRF page **or SAE form**. There may be instances when copies of medical records for certain cases are requested by eg, **the SAE coordinator** ~~SGS~~ or the sponsor. … **Assessment of Event Severity:** **The investigator will make an assessment of severity for each AE and SAE reported during the trial.** All events (AEs and SAEs) observed will be graded using the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 5.0. ~~The NCI CTCAE is a descriptive terminology, which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.~~ 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 CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on~~ the following general guideline: • Grade 1: … • Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living **(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 activities of daily living **(ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)**. • Grade 4: …~~;~~ **or** urgent intervention indicated. **Assessment of Causality:** The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE~~.~~**, using 1 of the following categories:** • **Not related: events can be classified as "not related" if there is not a reasonable possibility that the IMP caused the AE.** • **Unlikely related: an "unlikely" relationship suggests that only a remote connection exists between the IMP and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state,**	

Section(s)	Change	Rationale
	or reaction to concomitant medication, appear to explain the reported AE. • **Possibly related: a "possible" relationship suggests that the association of the AE with the IMP is unknown; however, the AE is not reasonably supported by other conditions.** • **Probably related: a "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.** • **Related: a "related" relationship suggests that the AE follows a reasonable temporal sequence from administration of IMP, it follows a known or expected response pattern to the IMP, and it cannot reasonably be explained by known characteristics of patient's clinical state.** **In final evaluation for reporting, the assigned relationship, as per Council for International Organizations of Medical Sciences (CIOMS), will be converted into a "binary determination" as follows: Events with an assigned relationship of "unrelated" or "unlikely related" will be grouped into the "unrelated" category. Events with an assigned relationship of "related," "possibly related," or "probably related" will be grouped into the "related" category.** … There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to **the SAE coordinator/sponsor** ~~SGS~~. However, it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to **the SAE coordinator/sponsor** ~~SGS~~. … **Follow-up of AE and SAE:** The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by **the SAE coordinator/sponsor** ~~SGS~~ to elucidate the nature and/or causality of the AE or SAE as fully as possible. … Thereafter, new/updated information will be collected in the safety database at **the SAE coordinator** ~~SGS~~. The investigator will submit any updated SAE data **to the SAE coordinator** ~~SGS~~ within 24 hours of receipt of the information.	

Section(s)	Change	Rationale
	• Section 11.4.4 "Reporting of SAEs SAE Reporting via Paper Form: ~~Facsimile transmission of the paper SAE form is the preferred method to transmit this information to SGS.~~ ~~In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.~~ ~~Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.~~ All SAEs will be recorded **(within 24 hours)** on the paper SAE report form and the AE form in the eCRF. The investigator or designated site staff should check that all entered data are consistent. An alert email for the SAE report in the eCRF will then automatically be sent by email to the ~~sponsor's designated CRO~~ **SAE coordinator's** safety mailbox via the electronic data capture (EDC) system. The paper SAE report form should be faxed or emailed to the ~~sponsor's designated CRO~~ **SAE coordinator**.	
• Section 11.11	Throughout the Appendix: Efficacy is planned to be assessed using a video interview between the evaluating physician and the patient. However, it has been added that a telephone interview can be performed instead, in case a video interview is not possible. Scheme for Home Visits: Tasks for Treating Physician • **Confirmation that IMP can be administered** IMP Administration IMP can be administered at home by a qualified person (eg, home nurse) **after confirmation of the treating physician**.	Further clarification how to perform a home visit during the COVID-19 pandemic
• Section 11.11.1	Section 11.11 "Schedule of Activities (SoA) During COVID-19 Pandemic": • Section 11.11.1 "SoA for Screening, Run-in, and Stage A During COVID-19 Pandemic": – Training for IMP self-administration during the second, third, and fourth visits of Stage A will only be performed if feasible during the COVID-19 pandemic (indicated in black open circles in the Schedule of Activities) and are not mandatory (indicated in red solid dots in the Schedule of Activities); these trainings are only mandatory in the "normal situation" (as indicated in the Schedule of Activities in Section 1.3.1). – Footnote d: ***Note:* Patients with ECI preferably have a combined visit that includes the last visit of Stage A (EOSA) and the first visit of Stage B (D1B). In this case, all assessments at EOSA are mandatory.**	Correction that training for IMP self-administration at certain visits of Stage A is not mandatory for special visits (as described in Appendix 11) during the COVID-19 pandemic. Explanation which assessments are mandatory at the last visit of Stage A for patients who start Stage B, and at the last visit of Stage B

Section(s)	Change	Rationale
	• Section 11.11.1 "SoA for Stage B and Follow-up During COVID-19 Pandemic": – Footnote b: Patients who will roll over to the open-label extension trial, will have a combination of this last visit in the ARGX-113-1802 trial and the first visit of the open-label extension trial ARGX-113-1902. [redacted]	for patients who roll over to the open-label extension trial.
• Section 11.12	Section 11.12 "Appendix 12: Administrative Structure": • Project Management and Clinical Research Organization (except for Georgia), and Safety Reporting for ~~Serbia and~~ Japan • Pharmacovigilance (Except Safety Reporting for ~~Serbia and~~ Japan) ~~and Coordination of Data Safety Monitoring Board~~ **Parexel International 8 Federal Street, Billerica, MA 01821, United States of America** ~~SGS Life Sciences (SGS LS), a division of SGS Belgium NV, Generaal de Wittelaan 19A b5, 2800 Mechelen, Belgium~~ • Data Management and Biostatistics**, and Coordination of Data Safety Monitoring Board**	Updated administrative structure
• Section 12	• Section 12 "References": Efgartigimod (ARGX-113) Investigator's Brochure, version ~~7~~**9**.0, **November 2020** ~~June 2019~~. **Clinical Trials Facilitation and Coordination Group, CTFG 21/09/2020. Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf, accessed 10 November 2020.**	Updated reference to new edition of IB and to contraception/pregnancy recommendations

General Amendment 2, General Protocol Version 3.0:

The major changes from Protocol Version 2.0 compared to Protocol Version 3.0 are summarized in the table below. Deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text. Minor administrative editorial changes (eg, to improve readability or correct spelling mistakes) are not summarized in the following table:

Summary of Changes Between Protocol Version 2.0 and Protocol Version 3.0

Section(s)	Change	Rationale
• Page 2, Section 11.11 "Appendix 11"	A notification has been added in the beginning of the protocol (on page 2) that adaptations can be made during the COVID-19 pandemic.	Based on this risk-benefit assessment, the clinical study ARGX-113-1802 can be conducted, however, because of the pandemic it may not be possible to

Section(s)	Change	Rationale
	An Appendix has been added to this protocol with the minimum assessments required to perform the trial during the COVID-19 pandemic in case the patient cannot attend the visit at the hospital site.	perform all assessment as planned for this trial (as outlined in the Schedule of Activities). Therefore, an Appendix to the protocol for this trial has been developed, with the minimum assessments required to guarantee the safety and well-being of the patients during the trial, and to secure the collection of the critical parameters for analysis.
• Synopsis	Stage A ~~No formal hypothesis testing will be conducted for Stage A.~~ For the interim analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact Clopper-Pearson 90% 1-sided lower CI. Stage B Alternative hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is $\not\leq 1$ (ie, hazard ratio $\not\leq 1$).	Typo –update was left out from the synopsis during previous protocol amendment (when changed were made in Section 10.2 of the protocol).
• Synopsis, Section 1.3.1, Section 5.1.1.3, Section 5.1.2, Section 7.1.1.	• Synopsis and Section 5.1.1.3: … documented evidence for worsening on the total adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, further referred to as "adjusted INCAT score." within 3 months prior to screening is available **compared to previous adjusted INCAT score within 6 months prior to screening**. • Section 1.3.1 (SoA footnote "a"), Section 5.1.2, and Section 7.1.1: … documented evidence for worsening on the adjusted INCAT score within 3 months prior to screening is available **compared to previous adjusted INCAT score within 6 months prior to screening**.	Clarification that for "documented evidence for worsening on the adjusted INCAT score," the reference INCAT score should be 6 months before screening.
• Synopsis, Section 5.1	• Synopsis: - Run-in period: ~~4—~~ **up to** 12 weeks … • Section 5.1: - Run-in period: ~~4—~~**up to** 12 weeks …	Correction that the run-in period is up to 12 weeks and that there is no minimum of 4 weeks required in the run-in period (as was erroneously stated at some places in the protocol) before going to Stage A of the trial.
• Footnotes from Schedules of Activities and Section 9.5.1	• Schedule of Activities for Screening, Run-in, and Stage A: g. Includes physical examination, height, weight, **semi-**supine blood pressure~~,~~ **and** heart rate, and body temperature. h. Includes physical examination, weight, **semi-**supine blood pressure~~,~~ **and** heart rate, and body temperature.	The vital signs blood pressure and heart rate are measured in a semi-supine position.

Section(s)	Change	Rationale
	• Schedule of Activities for Stage B and Follow-up: e. Includes physical examination, weight, **semi**-supine blood pressure~~,~~ **and** heart rate, and body temperature. • Section 9.5.1 "Vital Signs and Physical Examination": The assessment of vital signs (~~supine~~ systolic and diastolic blood pressure, heart rate, and body temperature) will be performed at the time points indicated in the SoA (see Section 1.3). Vital signs will be measured before blood collections. Blood pressure (~~supine~~ systolic and diastolic) and heart rate will be measured using standard equipment in semi-supine position after having rested for at least 5 minutes.	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
• Section 5.1.1.1, Section 11.1.3	• Section 5.1.1.1 "Informed Consent": The patient must sign the informed consent form (ICF) prior to any trial-related assessment. In case the patient is physically ~~non-~~**in**capable to sign the ICF, a legally acceptable representative **(according to local regulations)** can sign for him/her.	Adapted because "legal representatives" are not allowed in some countries.

Section(s)	Change	Rationale
	• Section 11.1.3 "Informed Consent Process" … legally authorized representative **(according to local regulations)** …(3 times)	
• Section 5.1.4, Section 7.2	• Section 5.1.4 "Stage B" Patients with ECI during Stage A will be randomized at Stage B baseline (D1B) in a 1:1 ratio to receive weekly SC administrations of efgartigimod PH20 SC or ~~matching~~ placebo. • Section 7.2 "Preparation, Handling, Storage, Administration, and Accountability": **For Stage B, IMP will be provided in a blinded vial. The trained and authorized site staff will blind the syringe for administration using a yellow blinding foil covering the barrel of the syringe before withdrawing IMP from the blinded vial. The administration is then performed by the site staff who prepared the syringe.**	A completely matching placebo is currently not available; however, blinding will be ensured as described in Section 7.2.
• Synopsis, Section 6.2, Section 7.4.1, Section 7.4.2	• Synopsis and Section 6.2 "Exclusion Criteria": 12.**a. Patients who received a live-attenuated vaccine fewer than 28 days before screening. Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not exclusionary.** • Section 7.4.1 "Permitted Medication": Any kind of vaccination**, except for live-attenuated vaccines,** is allowed at the discretion of the investigator. • Section 7.4.2 "Prohibited Medications": • **Live-attenuated vaccines (Note: Receiving an inactivated, sub-unit, polysaccharide, or conjugate vaccine any time before screening is not prohibited).**	Live-attenuated vaccines are not allowed from 28 days before screening through 28 days after the last IMP dose, consistent with the updated text in the efgartigimod Investigator's Brochure (Version 8.0).
• Synopsis and Section 6.2	~~Use of an investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to first IMP administration.~~ (Note: This exclusion criterion is replaced by the exclusion of patients who received a live-attenuated vaccine fewer than 28 days before screening; see above [ie, exclusion criterion 12.a.])	Exclusion criterion #12 is captured already in #9: "Within 3 months [or 5 half-lives of the drug, whichever is longer] before screening: plasma exchange or immunoadsorption, any concomitant Fc containing therapeutic agents or other biological, or any other investigational product."
• Section 7.4	Clinically relevant prior treatments received by the patient including: • Previous treatments or procedures for CIDP ~~in the last 2 years~~ with patient's response and reason for changing treatment/dose ~~in the last 12 months~~.	All previous medications should be collected in order to check inclusion criterion #6 (which states that corticosteroids and/or IVIg or SCIg should have started within the last 5 years before screening).

Section(s)	Change	Rationale
• Section 8.3	• **(During Stage A only:) Adjusted INCAT deterioration of ≥2 points from Stage A baseline (D1A).**	Addition of withdrawal criterion, because it is unlikely that these patients will benefit from efgartigimod PH20 SC.
• Section 11.4.4	~~**SAE Reporting to SGS via an Electronic Data Collection Tool**~~ ~~The primary mechanism for reporting an SAE to SGS will be the electronic data collection tool.~~ ~~If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.~~ ~~The site will enter the SAE data into the electronic system as soon as it becomes available.~~ ~~After the trial is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.~~ ~~If a site receives a report of a new SAE from a trial patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off line, then the site can report this information on a paper SAE form (see next section) or to SGS by telephone.~~ ~~Contacts for SAE reporting can be found on the frontpage.~~ SAE Reporting ~~to SGS~~ via Paper Form ~~Facsimile transmission of the paper SAE form is the preferred method to transmit this information to SGS.~~ ~~In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.~~ ~~Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.~~ **All SAEs will be recorded on the paper SAE report form and the AE form in the eCRF. The investigator or designated site staff should check that all entered data are consistent. An alert email for the SAE report in the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the electronic data capture (EDC) system. The paper SAE report form should be faxed or emailed to the sponsor's designated CRO.**	Clarification of SAE reporting system.
• Section 11.12 "Appendix 12"	An Appendix has been added to this protocol with the administrative structure.	For completeness, the vendors contracted by argenx have been added.

General Amendment 1, General Protocol Version 2.0:

The major changes from Protocol Version 1.0 compared to Protocol Version 2.0 are summarized in the table below. Deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text. Minor administrative editorial changes (eg, to improve readability or correct spelling mistakes) are not summarized in the following table:

Summary of Changes Between Protocol Version 1.0 and Protocol Version 2.0

Section(s)	Change	Rationale
• General change throughout the protocol of primary endpoint of Stage B: Confirmation of deterioration in Stage B 3-7 days after the first adjusted INCAT deterioration of 1 point; and no confirmation needed in case of adjusted INCAT deterioration of ≥2 points	Stage B: Primary Endpoint: • Time to first ~~confirmed~~ adjusted-INCAT deterioration compared to Stage B baseline. *Note*: Time to first ~~confirmed~~ adjusted-INCAT deterioration is defined by the time from first dose of double-blind IMP to the first adjusted INCAT score increase of ≥1 point compared to Stage B baseline~~,~~ if the deterioration is confirmed at a consecutive visit ~~one week~~ **3-7 days** after the first adjusted INCAT score increase of ≥1 point. **For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required.**	The time window for confirmation of INCAT deterioration has been shortened to reduce the time of clinical deterioration, and offer follow-up treatment as soon as possible. The minimal interval is shorted to the shortest interval of IMP injection allowed in the protocol, ie, 3 days. The confirmation of clinical deterioration during Stage B for those patients with an adjusted INCAT increase of 2 points or more compared to Stage B baseline has been deleted to prevent further deterioration. It is considered to be more appropriate to give these patients the possibility to roll over immediately when this level of deterioration is observed or receive standard of care treatment.
• Title page	Addition of the logo of the trial.	Addition of the logo of the trial.
• Title page and signature pages	Moved the trial name 'ADHERE' to a separate row (ie, 'acronym: ADHERE') instead of adding this after the title.	The acronym is not part of the title of the trial.
• Section 1.3.1	k. These tests are ~~optional and are~~ only required for confirmation of improvement (for patients with improvement in the previous visit).	Update of footnote k of the Schedule of Activities for Screening, Run-in, and Stage A.
• General change throughout the protocol: The safety follow-up visit in Stage B should be performed 28 days after the last IMP dose	~~W48/ED +~~ 28 (±3) days **after last IMP dose** • Follow-up: 28 days after the last dose of investigational medicinal product (IMP) ~~or the Week 48 visit~~ if the patient does not intend to roll over into the open-label extension (OLE) trial ARGX-113-1902.	The safety follow-up visit in Stage B should be performed 28 days after the last IMP dose instead of 28 days after the week 48 visit. As the last IMP dose is administered at week 47, the safety follow-up visit should be performed at week 51, instead of week 52, and the total trial duration will be 80 weeks (instead of 81 weeks).

Section(s)	Change	Rationale
• Section 2.2	**A deterioration of the adjusted INCAT score is defined as an increase (ie, worsening) of 1 point on the adjusted INCAT score compared to Stage B baseline which is confirmed at a consecutive visit 3-7 days after the first adjusted INCAT score increase of 1 point. For patients with an increase of 2 or more points on the adjusted INCAT score compared to Stage B baseline, no confirmation is required.**	Addition of definition of adjusted INCAT deterioration
• Synopsis, Section 5.1.4, and Section 7.7	Patients completing week 48 **and in the opinion of the investigator benefit from trial treatment at week 48** or **patients** having an event of ~~confirmed~~ worsening on the adjusted INCAT score of ≥1 point or a worsening on the adjusted INCAT score of **≥2 points compared to Stage B baseline (for the latter, no confirmation is needed)** will be allowed to roll over to the open-label extension (OLE) trial **when they are receiving IMP**. Patients completing week 48 who will not roll over to the OLE trial as well as patients with an early discontinuation, will have a safety follow-up visit 28 days after ~~the week 48 visit (or 28 days after~~ the last IMP administration ~~if the patient is discontinuing from the trial)~~, will stop the trial, and will be treated as considered appropriate by the investigator. When 88 events have been observed for the primary endpoint **analysis of Stage B** (see sample size determination for Stage B in Section 10.3), then the trial will stop. In that case, patients in Stage A and Stage B will **perform an early discontinuation visit and patients who are receiving IMP will be given the opportunity to continue efgartigimod PH20 SC treatment in** ~~be allowed to roll over to~~ the OLE trial ~~at their next visit~~. **Patients who will not roll over to the OLE trial, will attend a follow-up visit 28 days after the last IMP dose.**	Better explanation when patient can roll over to the open-label extension trial and to make clearer that in case 88 events have been observed, an early discontinuation visit needs to be performed (and the patients can then roll over to open-label extension trial or have a follow-up visit after 28 days in case they will not roll over).
• Section 5.1.5	An unscheduled visit is to be planned for: 1) safety reasons, 2) assessment of ECMD during the run-in period, ~~and~~ 3) **assessment of efficacy during Stage B** (eg, confirmation of ~~clinical deterioration during Stage B~~ (**worsening** ~~in~~ **on the** adjusted INCAT score ~~by ≥~~ of 1 point), ~~if no trial visit is planned at that time,~~ **or 4) any other reason**.	Clarification when an unscheduled visit can be performed.
• Inclusion criterion #5 in synopsis and Section 6.1	5. An ~~adjusted~~ INCAT score ≥2, **with a score of 2 exclusively from leg disability**, ~~in at least one leg~~ at the first run-in visit (RI-V1; for patients entering run-in) or Stage A baseline (A-V1; for treatment-naïve patients with documented evidence for worsening on the total adjusted INCAT disability score within 3 months prior to screening).	During the trial, the total score for the deterioration is observed. For screening, the minimal INCAT score was set at ≥2, to make sure there is still room for improvement during IMP treatment. For a low INCAT score of 2, we want to make sure that these 2 points come from the leg (as was done the FORCIDP[1] trial in patients with CIDP).

Section(s)	Change	Rationale
		Furthermore, as this is the first INCAT assessment in the trial, "adjusted" is deleted.
• Exclusion criterion #11 in synopsis and Section 6.2	11. Patients with any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of **CIDP** ~~"trial indication."~~	Addition of the trial indication in the exclusion criterion.
• Section 3.1	The term chronic inflammatory demyelinating polyneuropathy (CIDP) has been used to identify ~~patients with~~ a chronically progressive or relapsing symmetric sensorimotor disorder with cytoalbuminologic dissociation and interstitial and perivascular endoneurial infiltration by lymphocytes and macrophages. A number of variants of CIDP have been described that have immune or inflammatory aspects and electrophysiologic and/or pathologic evidence of demyelination in common. No consensus exists on the best approach to the nomenclature of these disorders. CIDP variants include **disorders** ~~patients~~ with predominantly sensory symptoms, distal symmetric disorder (DADS), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) also known as Lewis-Sumner syndrome, and ~~those with~~ CIDP with associated central nervous system (CNS) demyelination or with other systemic disorders.[1,21] CIDP most commonly has an insidious onset with either a chronic progressive or a relapsing course. Occasionally, complete remission occurs. The estimated prevalence of CIDP is 1.8-8.9 per 100000.[20] CIDP may occur at any age, but it is more common in the fifth and sixth decades. **A r**~~R~~elapsing course is associated with younger age of patients (third and fourth decades). The most common treatments are currently immunosuppressive or immunomodulatory interventions. These agents include intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg), plasmapheresis, prednisone, azathioprine, methotrexate, mycophenolate, cyclosporine, and cyclophosphamide. Their use is based on the proposed pathogenesis of CIDP as an immune-mediated condition, though for some of these **agents**, there is no clear evidence of a beneficial treatment effect. **However, an unmet medical need exists for an efficacious treatment of CIDP with a more specific mechanism of action maintaining quality of life (QoL) at the highest levels for the longest**	Minor updates in the section "Trial Rationale" to align with the text for this section in the open-label extension trial.

Section(s)	Change	Rationale
	period possible, a favorable safety and tolerability profile, and more convenient administration that has a significantly lower impact on daily routines than that provided by current treatments. ~~However, an unmet medical need exists for an efficacious treatment of CIDP with a favorable safety and tolerability profile and more convenient administration than that provided by current treatments.~~ ~~It has been recognized from recent treatment trials that many CIDP patients are over-treated and have stable disease off-therapy, and there have been placebo response rates as high as 40%.[16,33] Therefore, there is an unmet need in CIDP for a treatment with a more specific mechanism of action, which allows to have a significantly lower impact on daily routines, maintaining quality of life at the highest levels for the longest period possible, with less adverse drug reactions and lower treatment burden.~~	
• Section 7.4.2	• Pulsed corticosteroids and oral daily corticosteroids ≤10 mg/day. **Note: If tapering is required, it should be initiated during the screening period according to local practice.** … If the administration of a non-permitted concomitant drug becomes necessary during the clinical trial, eg, because of AEs, the patient has **to discontinue IMP** ~~be withdrawn from the trial~~, as described in Section 8.2.	The note is added to clarify when tapering of the corticosteroids should be performed. In case non-permitted concomitant drug is taken, the patient has to discontinue IMP (not the trial).
• Section 9.1	• Mycobacterium tuberculosis (TB): **Patients with clinical symptoms/signs of TB cannot enter the trial.** TB test (Quantiferon) will be performed at screening **and may be repeated during the trial, if necessary**. ~~If positive at screening, the patient cannot enter the trial.~~ **If a negative Quantiferon test at screening turns positive during the trial, a clinical work up will be applied.** If clinical symptoms or signs of TB occur~~s~~, it will be reported as an AE and treated accordingly.	Text updated to only exclude patients with clinical symptoms/signs of TB to enter the trial.
• Section 9.4.2	The MRC sum score is evaluated bilaterally on 6 muscle groups of upper and lower limbs in order to obtain a summed score between 0 and 60: • **Arm** abductors~~ion of the arm~~ • **Elbow** flexors~~ion of the forearm~~ • **Wrist** extensors~~ion of the wrist~~ • **Hip** flexors~~ion of the leg or hip flexion~~ • **Knee** extensors~~ion of the knee~~	Updated to the original names of the movement of the muscles.

Section(s)	Change	Rationale
	• **Foot** dorsiflexors~~al flexion of the foot~~	
• Section 9.8	~~Visit Reminder~~/Patient ~~ID~~ Card	Deletion of "Visit Reminder" and "ID" as this will be called a "Patient Card" in this trial.
• Section 9.9	~~The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.~~	Sentence is deleted from the pharmacokinetic assessment section, as the actual date and time of collection of samples will not be recorded in the eCRF.
• Section 10.2	The statistical hypotheses were derived from the trial objectives as stated in Section 4. Stage A: • ~~No formal hypothesis testing will be conducted for Stage A.~~ For the interim analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact **one-sided** Clopper-Pearson 90% CI. For the final analysis, the percentage of ECI responders on efgartigimod PH20 SC will be summarized using an exact Clopper-Pearson 2-sided 95% CI. **This 95% two-sided Clopper-Pearson CI will be used to compare the results of this study with results obtained in historical controls such as the PATH trial (van Schaik et al, 2018)**[15] Stage B: • Null hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is 1 (ie, hazard ratio = 1). • Alternative hypothesis: The event rate of efgartigimod PH20 SC compared to placebo is ~~≤~~≠1 (ie, hazard ratio ~~≤~~≠1).	The statistical hypotheses section has been updated to better describe the currently planned analyses; ie, to compare Stage A with historical data using the Clopper-Pearson CI, and to correct that the hazard ratio is ≠1 as the hypothesis testing is two-sided.
• Section 10.4.2.2	• **Change from Stage A baseline over time for subjects randomized to efgartigimod PH20 SC in:** – **Adjusted INCAT score.** – **MRC sum score.** – **24-item I-RODS disability scores.** – **TUG score.** – **Mean grip strength assessed by Martin vigorimeter.**	Addition of a secondary efficacy endpoint to learn how subjects improve over longer time period (longer than the 4–12 weeks in Stage A) when treated with efgartigimod PH20 SC.
• Section 10.6	After the first 30 patients have reached the end of Stage A, an interim analysis will be performed and the proportion of patients with confirmed ECI will be calculated with the exact Clopper-Pearson 90% 1-sided lower CI. ~~If 19 of the 30 (63%) patients have a confirmed response, then there is 90% confidence that the true response rate is at least 50%.~~ **A non-binding futility rule will be used to guide continuation of the study. If 9 or less of the first 30 subjects have a confirmed ECI, the**	The language for the in interim analysis was modified to reflect that if ≤9 subjects of the first 30 subjects will have confirmed ECI, the recommendation will be to stop the trial.

Section(s)	Change	Rationale
	Clopper-Pearson 90% 1-sided lower CI will not exclude a rate of 21%, (placebo rate observed in ICE trial[16]), and the recommendation will be to stop the trial. The DSMB charter will contain full details on the non-binding futility rule and guidance to continue the trial. The decision to continue the trial will be advised by an independent DSMB (see Section 11.1.5) and the final decision will be taken by the sponsor.	
• Section 11.2 Appendix 2	Blood Screening for Infections: HIV§ (Ag/Ab test) **§ CD4 count to be analyzed in case of positive HIV (see exclusion criterion #7)**	Addition of footnote to HIV test (belonging to blood screening for infections) to make sure CD4 count is determined in case of a positive HIV test.
• Section 11.7 'Appendix 7'	**The scale is bilaterally applied to 6 muscle groups of the upper and lower limbs in order to obtain a summed score ranging from 0 to 60 for the MRC scale: 1) arm abductors; 2) elbow flexors; 3) wrist extensors; 4) hip flexors; 5) knee extensors; and 6) foot dorsiflexors.**	Addition of footnote to explain the MRC scale, which was erroneously deleted during the writing of the protocol.
• Section 12 'References'	**Hughes R, Dalakas M, Merkies I, et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicenter, randomized controlled trial. The Lancet Neurology 2018;17(8):689-698.**	Addition of a publication of the FORCIDP trial in patients with CIDP.

11.14. Appendix 14: Country-Specific Requirements

11.14.1. Denmark-Specific Protocol Requirements

The Denmark-specific protocol requirements are summarized in the table below. Changes from the global protocol are indicated as follows: deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text.

Denmark-specific Protocol Requirements

Section(s)	Change vs Global Protocol	Rationale
• Section 1.3.1, Section 7.1.2, Section 11.12	• Section 1.3.1 and Section 11.12 (Appendix 12): Schedule of Activities for Screening, Run-in, and Stage A, footnote belonging to IMP administration; addition of the following: **Patients will be monitored for at least 1 hour after each of their first 3 IMP administrations.** • Section 7.1.2 Stage A: Open-label; addition of the following: **Patients will be monitored for at least 1 hour after their first 3 IMP injections by a health care professional trained in the diagnosis and treatment of acute hypersensitivity reactions, with immediate access to equipment and medication to treat such reactions.**	Based upon feedback of the Danish Medicines Agency (DKMA), patients will be monitored for at least 1 hour after the first 3 SC injections with efgartigimod PH20 SC by a trained health care professional.

11.14.2. Germany-Specific Protocol Requirements

The Germany-specific protocol requirements are summarized in the table below. Changes from the global protocol are indicated as follows: deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text.

Germany-specific Protocol Requirements

Section(s)	Change vs Global Protocol	Rationale
• Throughout the protocol (ie, Synopsis, Section 1.3 [in both Schedules of Activities], Section 5.1, Section 5.1.3, Section 5.1.4, Section 5.1.6, Section 5.4.2, Section 5.5, Section 7.1.2, Section 8.2, Section 8.3, Section 11.12)	• Extension of safety follow-up period from 28 days to 42 days: …~~28~~ **42** days…	Based upon feedback of the German Competent Authority (Paul Ehrlich Institut), the safety follow-up duration is extended from 28 days to 42 days.
• Synopsis, Section 5.1	• Synopsis: The maximum total trial duration is **82**~~80~~ weeks with a maximum of 61 weeks on IMP • Section 5.1 "Overall Design": Total trial duration for each patient can be up to **82**~~80~~ weeks with a maximum of 61 weeks on IMP.	Correction; The total trial duration is 82 weeks instead of 80 weeks, because the follow-up period has been extended from 28 days to 42 days.

11.14.3. Japan-Specific Protocol Requirements

The Japan-specific protocol requirements are summarized in the table below. Changes from the global protocol are indicated as follows: deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text.

Japan-specific Protocol Requirements

Section(s)	Change vs Global Protocol	Rationale
• Synopsis and Section 6.1	Addition of the following inclusion criterion: **10. For Japanese patients enrolled in sites in Japan only: A Japanese patient is defined as a patient whose parents and 4 grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of >10 years, and currently lives in Japan.**	The definition of a Japanese patient was added for clarification and completeness.
• Section 1.3.1, Section 9.9, Section 11.12.1	Addition of the following in the: - Schedule of Activities in Section 1.3.1 and Section 11.12.1 (added as a footnote to Blood sampling for PK and PD analysis at visits A-V1 and A-V4); and - Section 9.9 Pharmacokinetics: **Two additional PK samples will be taken; ie, one sample 48 to 96 hours after the 1st IMP injection and one sample 48 to 96 hours after the 4th IMP injection in approximately 10 Japanese patients in Stage A. Note that no additional PD samples will be taken at these timepoints.** **See also below in the Japan-specific SoA**	As a result of the outcome of the PMDA consultation, there will be additional PK sampling points around the time of the anticipated maximum concentration of efgartigimod during Stage A of the trial to better characterize the PK of efgartigimod in Japanese patients.
• Section 1.3 and Section 11.12.1	• Schedule of Activities for Screening, Run-in, and Stage A: - Additional samples for blood & urine clinical laboratory safety tests at the 9th visit of Stage A, ie, visit A-V9 (Day 57). • Schedule of Activities for Stage B and Follow-up: - Additional samples for blood & urine safety tests at the 2nd visit of Stage B, ie, visit B-V2 (Week 4).	Based upon feedback from the PMDA, extra samples for blood and urine clinical laboratory safety tests will be taken. This sampling regimen allows weekly follow-up for the first 4 weeks of IMP dosing, and monthly assessments for the next few months, depending on the number of weeks a patient will be in Stage A. Once a patient is established into the treatment regimen in Stage B, laboratory safety tests will be performed every 3 months. Note that additional laboratory safety tests can be requested by the investigator (eg, in case of any abnormality).
• Section 1.3, Section 5.1.3. Section 5.1.4, Section 7.2, Section 11.12.1	• Section 1.3.1: Schedule of Activities for Screening, Run-in, and Stage A; addition of the following in footnote to IMP administration: … **Note: Patients will be asked to remain at the site for at least 1 hour after the end of the first 2 IMP injections (ie, at visits A-V1 and A-V2) and for at least 15 minutes after the end of the following IMP injections (from visit A-V3 onwards) in order to observe the patients for adverse events.**	Based upon feedback from the PMDA, patients will be observed for adverse events after the end of each IMP injection for at least 1 hour (for the first 2 injections) or for at least 15 minutes (after the following injections).

Section(s)	Change vs Global Protocol	Rationale
	• Section 1.3.2: Schedule of Activities for Stage B and Follow-up; addition of the following in footnote to IMP administration: … **Note: In order to observe the patients for adverse events, patients will be asked to remain at the site for at least 15 minutes after the end of each IMP injection administered at the site; in case of IMP administration by a home nurse, the home nurse will observe the patients for adverse events after each IMP injection.** • Section 5.1.3 Stage A; addition of the following: … **Patients will be asked to remain at the site for at least 1 hour after the end of the first 2 IMP injections (ie, at visits A-V1 and A-V2) and for at least 15 minutes after the end of the following IMP injections (from visit A-V3 onwards) in order to observe the patients for adverse events.** … • Section 5.1.4 Stage B; addition of the following: … **Patients will be asked to remain at the site for at least 15 minutes after the end of each IMP injection administered at the site in order to observe the patients for adverse events; in case of IMP administration by a home nurse (see below), the home nurse will observe the patients for adverse events after each IMP injection.** … • Section 7.2 Preparation, Handling, Storage, Administration, and Accountability; addition of the following: … **In order to observe the patients for adverse events, patients will be asked to remain at the site for at least 1 hour after the end of the first 2 IMP injections (ie, at visits A-V1 and A-V2 of Stage A) and for at least 15 minutes after the end of the following IMP injections (from visit A-V3 of Stage A onwards and during Stage B) after each IMP injection administered at the site; in case of IMP administration by a home nurse, the home nurse will observe the patients for adverse events after each IMP injection.** … • Section 11.12.1 (in "Appendix 12"): Schedule of Activities for Screening, Run-in, and Stage A; addition of the following in footnote to IMP administration: … **Note: In order to observe the patients for adverse events, patients will be asked to remain at the site for at least 1 hour after the end of the first 2 IMP injections (ie, at visits A-V1 and A-V2) and for at least 15 minutes after the end of the following IMP injections (from visit A-V3 onwards) for each IMP injection that is administered at the site; in case of IMP administration by a home nurse, the home nurse will observe the patients for adverse events after each IMP injection.** • Section 11.12.1 (in "Appendix 12"): Schedule of Activities for Stage B and Follow-up; addition of the following in footnote to IMP administration: … **Note: In order to observe the patients for adverse events, patients will be asked to remain at the site for at least 15 minutes after the end of each IMP injection administered at the site; in case of IMP administration by a home nurse, the home nurse will observe the patients for adverse events after each IMP injection.**	

Japan-specific SoA for Screening, Run-in, and Stage A:

Additional PK sampling at visits A-V1 and A-V4 (see footnote §):

	Screening ≤28 days	Run-in Period ≤12 weeks		Stage A: Open-Label Period ≤12 Weeks (With Optional 1 Additional Week)																Unsche-duled	Safety Follow-up
		RI-V1	RI-V2 to RI-V4	A-V1		A-V2	A-V3	A-V4		A-V5	A-V6	A-V7	A-V8	A-V9	A-V10	A-V11	A-V12	A-V13 (Addi-tional)	EOSA/ ED	UnschV	28 (±3) Days After Last IMP Dose
	Up to 28 days			D1A	D1A + 48 to 96 hours	D8	D15	D22	D22 + 48 to 96 hours	D29	D36	D43	D50	D57	D64	D71	D78	D85			
Assessment/Procedure		±0 days	±2 days	±0 days		±2 days	±2 days	±2 days		±2 days											
Blood sampling for PK and PD analysis				●	●§	●	●	●	●§	●	●	●	●	●	●	●	●	●	●	●	●

§ Two additional PK samples will be taken; ie, one sample 48 to 96 hours after the 1st IMP injection and one sample 48 to 96 hours after the 4th IMP injection in approximately 10 Japanese patients in Stage A. Note that no additional PD samples will be taken at these timepoints.

11.14.4. UK-Specific Protocol Requirements

The UK-specific requirements are summarized in the table below. Changes from the global protocol are indicated as follows: deleted text is indicated in strikethrough; a bold and underlined font is used to indicate added text.

UK-specific Protocol Requirements

Section(s)	Change vs Global Protocol	Rationale
•Section 5.2	**In the PATH trial, the median time to relapse in the placebo arm was 3 to 4 months and at the end of the 24 weeks of double-blind phase, 37% of placebo patients had not yet deteriorated based on the adjusted INCAT score. It is anticipated that efgartigimod may induce a greater reduction of autoantibodies. Therefore, sufficient time is required to allow enough cases of adjusted INCAT deteriorations (events) to occur for the primary efficacy analysis. For this reason, the double-blind phase (Stage B) is planned with a duration of 48 weeks. This duration will allow a potential longer carry-over effect from Stage A in addition to the median 3 to 4 months of relapse time observed in the placebo group in the PATH trial. The 48-week duration is expected to allow the differences between active and placebo to become apparent. The current assumption is a 2-fold difference between time to deterioration of the two treatment groups. The trial is powered based on the number of events (88; see Section 10.3). The number of patients enrolled, the estimated relapse rate, and the duration of 48 weeks are expected to allow the sponsor to come to a satisfactory conclusion of the trial.**	Based upon feedback of the MHRA, an explanation has been added for the duration of up to 48 weeks for Stage B of the trial (with double-blind, randomized-withdrawal treatment of efgartigimod PH20 SC or of placebo).
•Section 8.2	• Psychiatric conditions. ***Note**: In the case of severe depression, suicidal ideation, or attempted suicide, trial medication must be at least temporarily interrupted until the patient's psychiatric condition has been fully evaluated. ~~A~~ **by a** psychiatrist ~~should be consulted whenever necessary~~. Treatment may be resumed only **when psychiatric condition has been excluded and** ~~after consultation~~ with ~~the~~ sponsor**'s agreement**.*	Based upon feedback of the MHRA, in case of possible depression, the trial medication will be discontinued, and the patient will be referred to psychiatrist before trial medication can be resumed.
•Section 8.2, Section 8.3	• Section 8.2 Permanent Early Discontinuation of IMP + Section 8.3 Early Withdrawal From the Trial; the following applies to both sections: It is the investigator's decision, and not the sponsor's representative (eg, medical monitor or medical director) whether treatment and/or participation in the trial should continue or not if the treatment and/or trial discontinuation criteria are fulfilled as required per protocol.	Based upon feedback of the MHRA, in alignment with GCP ICH guidance, the investigator is responsible for all trial-related medical decisions

12. REFERENCES

1. Hughes R, Dalakas M, Merkies I, et al. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicenter, randomized controlled trial. *Lancet Neurol*. 2018;17(8):689-698.
2. EFNS Task Force. Members of the Task Force: Van den Bergh PYK, Hadden RDM, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society — First Revision. *Eur J Neurol.* 2010;17:356-363.
3. Gorson KC, van Schaik IN, Merkies ISJ, et al. Chronic inflammatory demyelinating polyneuropathy disease activity status: recommendations for clinical research standards and use in clinical practice. *J Peripher Nerv Syst.* 2010;15:326-333.
4. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology*. 2015;85:498-504.
5. Lewis RA. Chronic inflammatory demyelinating polyneuropathy. *Curr Opin Neurol.* 2017;30(5):508-512.
6. Laughlin RS, Dyck PJ, Melton LJ, et al. Incidence and prevalence of CIDP and the association of diabetes mellitus. *Neurology*. 2009;73(1):39-4.
7. Mathey EK, Park SB, Hughes RAC, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. *J Neurol Neurosurg Psychiatry.* 2015;86(9):973-985.
8. Kieseier BC, Mathey EK, Sommer C, et al. Immune-mediated neuropathies. *Nat Rev Dis Primers.* 2018;4(1):31.
9. Quast I, Cueni F, Nimmerjahn F, Tackenberg B, Lünemann JD. Deregulated Fcγ receptor expression in patients with CIDP. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(5):e148.
10. Zinman LH, Sutton D, Ng E, Nwe P, Ngo M, Bril V. A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IVIG in chronic inflammatory demyelinating polyneuropathy. *Transfus Apher Sci*. 2005;33(3):317-24.
11. Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in Guillain-Barré syndrome. *J Peripher Nerv Syst*. 2012;17(1):62-71.
12. Vaccaro C, Zhou J, Ober RJ, Ward ES. Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels. *Nat Biotechnol.* 2005;23(10):1283.
13. Efgartigimod (ARGX-113) Investigator's Brochure, version 10.0, November 2021.
14. Recombinant Human Hyaluronidase PH20 (rHuPH20) Investigator's Brochure, version 10.0,February 2022.
15. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH):

a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2018;17(1):35-46.

16. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo controlled trial. *Lancet Neurol.* 2008;7(2):136-44.
17. Fujita A, Ogata H, Yamasaki R, et al. Parallel fluctuation of anti-neurofascin 155 antibody levels with clinico-electrophysiological findings in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Sci.* 2018;384:107-112.
18. Querol L, Rojas-García R, Diaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflamm.* 2015;2(5):e149.
19. Van Nes SI, Vanhoutte EK, van Doorn PA, et al. Rasch-built overall disability scale (R ODS) for immune-mediated peripheral neuropathies. *Neurology*. 2001;76:337-345.
20. Draak TH, Gorson KC, Vanhoutte EK, et al. Correlation of the patient's reported outcome Inflammatory RODS with an objective metric in immune mediated neuropathies. *Eur J Neurol*. 2016;23(7):1248-1253.
21. Timed Up and Go (TUG) test. Minnesota Falls Prevention. 2010 02 16. Available at: http://www.mnfallsprevention.org/professional/assessmenttools.html, accessed 10 June 2019.
22. EuroQol EQ-5D instruments. Available at: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/, accessed 12 June 2019.
23. [redacted]
24. [redacted]
25. [redacted]
26. [redacted]
27. [redacted]
28. [redacted]
29. [redacted]

30. [redacted]

31. CDER Guidance for Industry. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Draft guidance, Revision 1, August 2012.

32. Simon GE, Rutter CM, Peterson D, et al. Does response on the PHQ-9 depression questionnaire predict subsequent suicide attempt or suicide death? *Psychiatry Serv.* 2013;64(12):1195-1202.

33. ICH E9 guideline. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials; E9. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Current Step 4 version, dated 5 February 1998.

34. Clinical Trials Facilitation and Coordination Group, CTFG 21/09/2020. Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1. Available at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf, accessed 10 November 2020.

35. Vanhoutte EK, Faber CG, van Nes SI, et al. Modifying the Medical Research Council grading system through Rasch analyses. *Brain*. 2012;135:1639-1649.

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