EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Vyvgart

International non-proprietary name: Efgartigimod alfa

Procedure No. EMEA/H/C/005849/II/0020

Marketing authorisation holder (MAH) Argenx

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List of abbreviations

Abbreviation	Expansion
1802	ARGX-113-1802
ACE	affinity capture elution
ADA	antidrug antibody(ies)
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
aINCAT	adjusted INCAT
ALP	alkaline phosphatase
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration-time curve from zero to infinite time
$AUC_{(ss)}$	area under the concentration-time curve over a dosing interval (at steady state)
$AUEC_{(ss)}$	area under the effect curve (at steady-state)
BEAD	biotin-drug extraction with acid dissociation
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
BPI-SF	Brief Pain Inventory – Short Form
CDAS	CIDP Disease Activity Status
CIDP	Chronic inflammatory demyelinating polyneuropathy
CL	clearance
C_{max}	maximum observed serum concentration
$C_{max,ss}$	maximum observed serum concentration at steady-state
CTCAE	common terminology criteria for adverse events
C_{trough}	concentration at the end of a dosing interval
$C_{trough,ss}$	trough concentrations at steady-state
CV	coefficient of variation
DBP	diastolic blood pressure
DDS	Drug Development Solutions
EAN/PNS	European Academy of Neurology/Peripheral Nerve Society
EC_{50}	half-maximal effective concentration (potency)
ECG	electrocardiogram
ECI	evidence of clinical improvement
ECLIA	electrochemiluminescence immunoassay
ECMD	evidence of clinically meaningful deterioration
efgartigimod PH20 SC	efgartigimod for SC administration coformulated with rHuPH20
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
E_{max}	maximal reduction from baseline/maximal effect
ER	event rate
EQ-5D-5L	EuroQol 5 dimensions and 5 levels health-related quality-of-life questionnaire
EU	European Union
(h)FcRn	(human) neonatal crystallizable fragment receptor
FDA	United States Food and Drug Administration
gMG	generalized myasthenia gravis

HADS	Hospital Anxiety and Depression Scale
(H)(M)(L)QC	(High)(Mid)(Low)Quality Control
HR	hazard ratio
IA(1)	interim analysis (1)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig(G)	immunoglobulin (γ)
IIV	inter-Individual Variability
IMP	investigational medicinal product
INCAT	inflammatory neuropathy cause and treatment
IND	investigational new drug
IPR	important potential risk
I-RODS	inflammatory Rasch-built Overall Disability Scale
ISR	incurred sample reanalysis
ISS	integrated summary of safety
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
Ka	absorption rate constant
Keo	delay rate constant
kout	degradation rate constant
MAH	marketing authorisation holder
MedDRA	Mmedical Dictionary for Regulatory Activities
MRC	Medical Research Council
N	number of participants
NAb	neutralizing antibody(ies)
NC	not calculated
OLE	open-label extension
P25	25th percentile
P50	50th percentile
P75	75th percentile
PB	pooling block
PBO	placebo
pcVPC	prediction corrected visual predictive check
PD	pharmacodynamic(s)
PB	pooling blook
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
placebo PH20 SC	placebo for SC administration coformulated with rHuPH20
PLEX	plasma exchange
PRO	patient-reported outcome
PT	preferred Term
PYFU	participant years of follow-up
QTcF	Fridericia corrected QT interval
rHuPH20	recombinant human hyaluronidase PH20
ROW	rest of world
RMM	risk minimization measures
RMP	risk management plan
RSE	relative standard error

RT-FSS	Rasch-transformed-Fatigue Severity Scale
SAE	serious adverse event
SAF	safety analysis set
SAF-A	stage A safety analysis set
SAF-B	stage B safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SCIg	subcutaneous immunoglobulin
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SOC	System Organ Class
TSQM-9	(9-item) Treatment Satisfaction Questionnaire for Medication
TUG	timed Up and Go
US	United States
V1	central volume of distribution
V2	volume of the second compartment
V2/V3	peripheral volume of distribution; volume of the second/third compartment
V3	volume of the third compartment

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Argenx submitted to the European Medicines Agency on 5 June 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) with active disease despite treatment with corticosteroids or immunoglobulins for Vyvgart, based on final results from study ARGX-113-1802; this is a pivotal study to investigate the efficacy, safety and tolerability of efgartigimod PH20 SC in adult patients with CIDP; and based on interim results from study ARGX-113-1902; this is an open-label extension study of the ARGX-113-1802 trial to investigate the long-term safety, tolerability and efficacy of efgartigimod PH20 SC in patients with CIDP.
As a consequence, sections 4.1, 4.2. 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Vyvgart, was designated as an orphan medicinal product EU/3/21/2555 on 14 January 2022. Vyvgart was designated as an orphan medicinal product in the following indication: treatment of chronic inflammatory demyelinating polyneuropathy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Vyvgart as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/vyvgart

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0443/2021 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	5 June 2024
Start of procedure:	22 June 2024
Rapporteur's preliminary assessment report circulated on:	20 August 2024
PRAC Rapporteur preliminary assessment report	23 August 2024
PRAC Rapporteur updated assessment report	28 August 2024
PRAC RMP advice and assessment overview adopted by PRAC	5 September 2024
Rapporteur's updated assessment report circulated on	12 September 2024
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2024
MAH's responses submitted to the CHMP on	14 November 2024
Rapporteur's preliminary assessment report circulated on:	20 December 2024
PRAC Rapporteur preliminary assessment report circulated on:	6 January 2025
PRAC Rapporteur updated assessment report circulated on:	9 January 2025
PRAC RMP advice and assessment overview adopted by PRAC	16 January 2025
Rapporteur's updated assessment report circulated on	24 January 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 January 2025
MAH's responses submitted to the CHMP on	24 February 2025
Rapporteur's preliminary assessment report circulated on:	24 March 2025
PRAC Rapporteur preliminary assessment report circulated on:	n/a
PRAC Rapporteur updated assessment report circulated on:	n/a
PRAC RMP advice and assessment overview adopted by PRAC	n/a

Timetable	Actual dates
Rapporteur's updated assessment report circulated on:	16 April 2025
SAG/Expert group/ Working Party experts meeting to address questions raised by the CHMP (Annex 6)	n/a
An Oral explanation took place on:	n/a
CHMP Opinion	25 April 2025

2. Scientific discussion

2.1. Introduction

As claimed by the MAH, the subject of this application is efgartigimod for SC administration coformulated with rHuPH20 in patients with CIDP with active disease despite treatment with corticosteroids or immunoglobulins. This coformulation is referred to as efgartigimod PH20 SC. Efgartigimod alfa (ARGX-113) is a human IgG1 antibody Fc fragment, which is a natural FcRn ligand (neonatal fragment crystallizable receptor). Engineered for increased FcRn affinity at both physiological and acidic pH, efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated IgG recycling and increasing IgG degradation. By blocking FcRn, efgartigimod reduces the levels of circulating disease-causing IgG antibodies.

2.1.1. Problem statement

Disease

CIDP (chronic inflammatory demyelinating polyneuropathy) is a severe, debilitating, progressive autoimmune disease of the peripheral nervous system, characterized by muscle weakness and sensory disturbance caused by peripheral nerve demyelination.

State the claimed the therapeutic indication

Vyvgart is indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) with active disease despite treatment with corticosteroids or immunoglobulins.

Epidemiology

The estimated prevalence of CIDP ranges from 0.8 to 8.9 per 100 000 persons. The incidence and prevalence of CIDP increase with age, with a crude incidence rate of 0.73 per 100 000 person-years in people over the age of 55

Aetiology and pathogenesis

Though the aetiology of the CIDP is unknown, several lines of evidence indicate that both cellular and humoral components of the immune system are involved in the pathophysiology of CIDP. Increasing evidence points to the central role of IgG autoantibodies, including the passive transfer of disease by

sera or IgG from patients with CIDP in experimental animal models, the effectiveness of PLEX (plasma exchange) and immunoadsorption for treating patients with CIDP, and the presence of IgG antibodies against components of myelinated nerves.

Clinical presentation, diagnosis and prognosis

CIDP is characterized by the chronic inflammatory demyelination of nerve fibers and symmetrical, motor-predominant peripheral neuropathy that produces both distal and proximal weakness or sensory deficits. CIDP is a heterogenous disorder in which most patients develop relatively symmetric motor and sensory symptoms in the proximal and distal upper and lower limbs (i.e., typical CIDP). However, distal predominant, asymmetric, pure motor, and pure sensory variants are also recognized as CIDP variants.

CIDP diagnosis is challenging, with misdiagnosis and delays in diagnosis being common. Diagnosis is based on clinical findings, electrophysiological study results suggesting peripheral nerve demyelination and supported by other criteria such as magnetic resonance imaging, ultrasound examination, and the response to immunotherapy. The key feature of CIDP recognized through electrophysiological studies is evidence of demyelination, although variable degrees of secondary axonal loss are also common and correlate with demyelination and a delayed start of treatment.

The extent of axonal loss is a primary determinant of long-term disability and irreversible nerve injury, and it may cause a substantial disease burden despite currently available treatments.

Management

Early administration of effective treatment is important for patients with CIDP. The goal is to stop the immune attack against the myelin sheath of peripheral nerves to minimize irreversible axonal degeneration. This can reduce symptoms, improve motor function, and prevent or minimize long-term disability. The most common treatments for CIDP are broadly immunosuppressive or immunomodulatory interventions and include high-dose IVIg (intravenous immunoglobulin), SCIg (subcutaneous immunoglobulin), corticosteroids, and PLEX. Other treatments, such as azathioprine, methotrexate, mycophenolate, cyclosporine, and cyclophosphamide, are used individually; however, the efficacies of these treatments have not been demonstrated in clinical studies. CIDP guidelines recommend IVIg or corticosteroids as the first-line treatment (Van den Bergh PYK et al. European Academy of Neurology / Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision Eur J Neurol. 2021;28(11):3556-3583).

Despite the current treatment options, including IVIg/SCIg and corticosteroids, many patients with CIDP continue to suffer from debilitating symptoms, have disease fluctuation and a substantial treatment burden, and often require chronic therapy. Current treatment options can be associated with lengthy infusion durations and severe complications such as thrombosis, acute renal dysfunction, and other undesirable effects such as weight gain and osteoporosis, limiting long-term administration. IVIg/SCIg are both dependent on plasma donors with potential for supply chain shortages.

2.1.2. About the product

Efgartigimod alfa (ARGX-113) is a human IgG1 antibody Fc fragment, which is a natural FcRn ligand, which outcompetes endogenous IgG binding. By blocking FcRn, efgartigimod reduces the levels of circulating disease-causing IgG antibodies.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

There have been no scientific advices prior to the extension of indication application. The Paediatric Committee granted a product specific waiver for efgartigimod for all subsets of the paediatric population for treatment of CIDP. Efgartigimod is likely to be ineffective or unsafe in part of all of the paediatric population and efgartigimod does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

No CHMP guidance exists on the treatment of CIDP.

2.1.4. General comments on compliance with GCP

The Applicant claimed that the conducted studies are considered compliant with GCP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

As per the EMA Guideline EMEA/CHMP/SWP/4447/00 corr. 2, Section 2, no environmental risk assessment studies were performed which is considered acceptable by CHMP. Efgartigimod is a monoclonal antibody which will be broken down by proteolysis, as such it will not alter the concentration or distribution of the substance in the environment. Therefore, efgartigimod is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of clinical studies supporting the application

Study status	Study design	Treatment (number of participants who received IMP)	Primary objective[a]
Participants with CIDP			
ARGX-113-1802 Completed	Phase 2 study of efgartigimod PH20 SC with 2 treatment stages: an open-label Stage A and a randomized-withdrawal, double-blinded, placebo-controlled Stage B	Stage A: • EFG PH20 SC (322 overall population; 139 pretreated population) Stage B: • EFG PH20 SC (111 overall population; 48 pretreated population) • Placebo PH20 SC (110 overall population; 47 pretreated population) EFG PH20 SC 1000 mg or placebo (with PH20) administered once weekly	Efficacy: • Stage A: Percentage of participants with confirmed ECI (ECI responders) • Stage B: Time to first occurrence of clinical deterioration[b] compared to Stage B baseline
ARGX-113-1902-IA1 Ongoing (clinical data cutoff date: 15 Jun 2023 for clinical data and 14 Apr 2023 for bioanalytical data)	Phase 2, open-label extension of ARGX-113-1802 with efgartigimod PH20 SC	EFG PH20 SC (228) EFG PH20 SC 1000 mg administered once weekly[c]	Safety
Healthy participants			
ARGX-113-1901 Completed	Phase 1, randomized, open-label, parallel-group study of efgartigimod SC comixed with rHuPH20	Single SC injection of: • EFG 750 mg + rHuPH20 2000 U/mL (8) • EFG 1250 mg + rHuPH20 2000 U/mL (9) • EFG 1750 mg + rHuPH20 2000 U/mL (8) • EFG 10 mg/kg body weight + rHuPH20 2000 U/mL (8)	PD
ARGX-113-1907 Completed	Phase 1, randomized, open-label, parallel-group study of efgartigimod IV and efgartigimod PH20 SC	4 once-weekly administrations of: • EFG PH20 SC 1000 mg (27) • EFG IV 10 mg/kg (27)	PD

2.3.2. Bioanalytical methods and validation

Posology

Dosage Form: Efgartigimod PH20 SC is formulated as a solution for injection. The volume of solution administered to participants is 5.6 mL, which delivers 1000 mg of efgartigimod.

Route of Administration: Efgartigimod PH20 SC is intended to be administered continuously as a once weekly subcutaneous dose of 1000 mg efgartigimod in the CIDP indication. This is different from the generalized Myasthenia Gravis (gMG) indication where Vyvgart is administered as once weekly SC injections in 4-week cycles. Subsequent treatment cycles should be administered according to clinical evaluation.

An overview of the PK, PD, and immunogenicity assessments in clinical studies of participants with CIDP is provided in Table 2.

Table 2: Overview of the PK, PD and immunogenicity assessments in participants with CIPD

Study	ARGX-113-1802 (pivotal study)	ARGX-113-1902 (open-label extension of ARGX-113-1802)
Design	Stage A: open-label Stage B: randomized-withdrawal design	Open-label
Study population	Participants with CIDP For participant disposition, refer to Module 5.3.5.1, ARGX-113-1802 CSR, Figure 2	Participants with CIDP For participant disposition, refer to Module 5.3.5.2, ARGX-113-1902-IA1 CSR, Table 4
Dosage and administration	Stage A: Weekly SC injections of efgartigimod PH20 SC 1000 mg for up to 12 weeks (with optional additional 1 week) Stage B: Weekly SC injections of efgartigimod PH20 SC 1000 mg or placebo for up to 48 weeks	Weekly SC injections of efgartigimod PH20 SC 1000 mg Substudy with 2 less frequent dosing regimens in a sequential manner, starting with once every 2 weeks and, if the participant remains stable, once every 3 weeks[a]
PK assessments	Stage A: Predose every week from weeks 0 to 12, at each unscheduled visit, at EOSA/ED, and at safety follow-up[b] In some Japanese participants, an additional PK sample was taken at 48 to 96 hours after the first and/or fourth efgartigimod PH20 SC injection Stage B: Predose every 4 weeks from weeks 0 to 48, at each unscheduled visit, at ED, and at safety follow-up[c]	First 48 weeks of treatment: Predose at weeks 0, 4, 12, 24, 36, and 48; each unscheduled visit; ED; and safety follow-up[d]
PD assessments	Total IgG Stage A: Predose every week from weeks 0 to 12, at each unscheduled visit, at EOSA/ED, and at safety follow-up[b] Stage B: Predose every 4 weeks from weeks 0 to 48, at each unscheduled visit, at ED, and at safety follow-up[c]	Total IgG First 48 weeks of treatment: Predose at weeks 0, 4, 12, 24, 36, and 48; each unscheduled visit; ED, and safety follow-up[d] After the first 48 weeks of treatment: Predose every 12 weeks, at each unscheduled visit, at ED, and at safety follow-up[d]
Immunogenicity of efgartigimod and rHuPH20	Stage A: Predose at weeks 0, 2, 4, and 8, at each unscheduled visit, at EOSA/ED, and at safety follow-up[b] Stage B: Predose every 4 weeks from weeks 0 to 48, at each unscheduled visit, at ED, and at safety follow-up[c]	First 48 weeks of treatment: Predose at weeks 0, 4, 12, 24, 36, and 48, at each unscheduled visit, at ED, and at safety follow-up[d,e]

EOSA=end of Stage A; IA=interim analysis; IgG=immunoglobulin γ; IMP=investigational medical product; PD=pharmacodynamic(s); PK=pharmacokinetic(s); rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous
a No PK, PD, and immunogenicity samples were available for participants in the substudy as of the data cutoff date of 14 Apr 2023 for bioanalytical samples.
b For participants who did not continue to Stage B and for participants who discontinued IMP, if IMP was stopped more than 28 days before the last study visit.
c For participants who did not continue to ARGX-113-1902 and for participants who discontinued IMP, if IMP was stopped more than 28 days before the last study visit.
d For participants who did not start a new 48-week treatment period and for participants who discontinued the study if IMP was stopped less than 28 days before the last study visit.
e Antibodies against rHuPH20 were only measured in samples from participants of mainland China. For participants from other countries, plasma samples to determine antibodies against rHuPH20 were collected, stored, and analyzed in case of safety concerns

Overview of clinical studies supporting the CIDP indication

The summary of biopharmaceutic studies and associated analytical methods will describe bioanalytical information for the CIDP indication using the efgartigimod PH20 SC formulation. In addition, relevant efgartigimod PH20 SC information from clinical studies in healthy participants is cross-referenced to the previously approved or submitted gMG IV or gMG SC applications.

The bioanalytical methods used for pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of efgartigimod PH20 SC are described for the following clinical studies involving participants with CIDP: ARGX-113-1802 (a completed pivotal study) and ARGX-113-1902 (an ongoing open-label extension study of ARGX-113-1802).

Interim bioanalytical data are included up to the bioanalytical data cutoff date of 14 Apr 2023. The study-specific bioanalytical method performance data are not available because the study is ongoing. Interim reports are not provided.

The bioanalytical methods used for evaluating the PK, PD, and immunogenicity of efgartigimod PH20 SC from phase 1 clinical studies in healthy participants are cross-referenced to the previously approved or submitted regional gMG IV or gMG SC applications, respectively: ARGX-113-1901 (gMG SC submission,), ARGX-113-1907 (gMG SC submission,), and ARGX-113-1702 (gMG IV submission).

Overview of Bioanalytical Methods and Validation

Pharmacokinetics

Serum efgartigimod concentrations are measured to assess the PK of efgartigimod PH20 SC. At clinically relevant doses, rHuPH20 is not measurable in the systemic circulation. Therefore, the PK of rHuPH20 was not assessed for the development of efgartigimod PH20 SC.

A sandwich immunoassay on the REDACTED system was used to determine efgartigimod concentrations in serum samples from ARGX-113-1802 and ARGX-113-1902. An immunoassay (ECLIA) method was used to measure the serum concentration of efgartigimod in participants from mainland China in ARGX-113-1802 and ARGX-113-1902.

The sandwich immunoassay is based on the capture of efgartigimod by biotin-labelled 2D11-His, followed by detection using a fluorescently-labelled 2D11-His. The assay was validated at Resolian (formerly known as DDS or LGC), including selectivity in sera from patients with CIDP. Supplemental validations were performed to assess selectivity in sera from Japanese individuals and long-term stability of efgartigimod in human serum.

The ECLIA method is based on the capture of efgartigimod by biotin-labelled 2D11-His, followed by detection using SULFO-TAG-labelled 2D11-His. The second assay was validated at REDACTED, and supplemental validations were performed to assess selectivity in sera from Chinese healthy participants and sera from Chinese patients with CIDP. The long-term stability of efgartigimod in human serum was also evaluated up to 18 months.

The Applicant also evaluated the cross-validation between the sandwich immunoassay and ECLIA methods to demonstrate how the PK results are related:

For this cross-validation study, a set of 90 human study samples from 30 healthy subjects were selected, reanalysed with the sandwich immunoassay and ECLIA methods and the results statistically compared. The samples were collected from clinical study ARGX-113-1901 entitled: "A phase 1, randomized, open-label, parallel-group trial to investigate the pharmacodynamics, pharmacokinetics, safety, and tolerability of different single subcutaneous dose levels of efgartigimod co-administered with rHuPH20 in healthy adult male subjects". Moreover, 11 Quality Control (QC) samples (10 spiked and 1 non-spiked)

at concentration levels within and above the range of quantification (600 – 40000 ng/mL) were analysed in both methods to evaluate the agreement.

A very high positive correlation of 0.994 was obtained by Pearson correlation coefficient. The incurred sample reanalysis (ISR) criterion was met for the paired ARGX-113 concentrations as obtained with both methods since more than 2 out of 3 samples, i.e. 79%, presented a difference within ±30%. The Bland-Altman analysis showed the presence of proportional bias which could also be noticed from the Deming regression: in the range of 3000 to 8000 ng/mL, a subset of samples presented high negative % differences (-70% to -40%), while most samples demonstrated % differences between -30% and -10%. The average difference was -26% with the ECLIA method reporting lower concentrations compared to the sandwich immunoassay method. Due to the presence of proportional bias and non-normality of % differences, the Bland-Altman interval and Deming regression do not give a correct representation.

In order to further investigate the observed findings, QC samples with a known concentration were provided to both laboratories for analysis. QC results obtained with the sandwich immunoassay method were all within 80% to 120% of the nominal concentration, while 4 out of 10 spiked QC samples in the ECLIA method demonstrated an accuracy below 80%. The ECLIA method reported lower concentrations across the entire concentration range compared to the sandwich immunoassay method.

In conclusion, the sandwich immunoassay and ECLIA methods presented a very high positive correlation regarding ARGX-113 concentrations across the entire concentration range thereby meeting the ISR criterion (i.e. 67% of the samples should present % differences within ±30%) . Both the human study samples and spiked QC samples confirmed that the ECLIA method was consistently reporting lower concentrations compared to the sandwich immunoassay method with an average difference of -26% for the study samples. The observations described above are supported by the QC sample results with the ECLIA method reporting consistently lower concentrations compared to the sandwich immunoassay method.

Information for the cross-validation is provided in Table 3.

Table 3: Summary Method Performance for Determination of Efgartigimod in Serum—Cross-Validation Method #3 and #5

Bioanalytical method validation report name and hyperlink	**Validation of a PK Assay for the Determination of ARGX-113 in Human Serum Using the [redacted] Platform (Module 5.3.1.4, LGC327456QB10)** **Validation of a Method for the Determination of ARGX-113 in Human Serum Using Electrochemiluminescence (ECL) (Module 5.3.1.4, 8471-441 addendum 01)** **Statistical Analysis of PK Cross-Validation Data for Efgartigimod Obtained With the [redacted] and ECLIA Methods at LGC UK and [redacted] Respectively (Module 5.3.1.4, ARGX-PTBA-0674)**				
Changes in method	Comparison of [redacted] method (Resolian[a], validated in report LGC327456QB10) with ECLIA method ([redacted], validated in report 8471-441 addendum 01)				
New validated assay range, if any	Range Resolian[a]: 200-10 000 ng/mL (LGC327456QB10) Range [redacted]: 200-6000 ng/mL (8471-441)				
Validation parameters	**Cross-validation performance**				**Source location**
Standard calibration curve performance during accuracy and precision runs	**Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ**	Resolian[a] Interrun accuracy	−1.1% to 1.4%		LGC327456QB10, Table 10
		[redacted] Interrun accuracy	−4.0% to 5.4%		8471-441 addendum01, Table 1
	Cumulative precision (%CV) from LLOQ to ULOQ	Resolian[a] Interrun precision	≤8.1%		LGC327456QB10, Table 10
		[redacted] Interrun precision	≤3.4%		8471-441 addendum 01, Table 1
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 5 QCs**	Resolian[a] Interrun accuracy	LLOQ (200 ng/mL) LQC (500 ng/mL) MQC (1500 ng/mL) HQC (7500 ng/mL) ULOQ (10 000 ng/mL)	−4.0% −4.0% −4.0% 1.7% 7.0%	LGC327456QB10, Table 55
		[redacted] Interrun accuracy	LLOQ LQC (600 ng/mL) MQC (2000 ng/mL) HQC (4500 ng/mL) ULOQ	NA −8.1% −4.5% −11.2% NA	8471-441 addendum 01, Table 4

Performance of QCs during accuracy and precision runs (continued)	**Precision (%CV)**	Resolian[a] Interrun precision	LLOQ (200 ng/mL) LQC (500 ng/mL) MQC (1500 ng/mL) HQC (7500 ng/mL) ULOQ (10 000 ng/mL)	9.1% 6.9% 4.8% 9.7% 17.6%	LGC327456QB10, Table 55
		[redacted] Interrun precision	LLOQ LQC (600 ng/mL) MQC (2000 ng/mL) HQC (4500 ng/mL) ULOQ	NA 6.1% 5.5% 7.6% NA	8471-441 addendum 01, Table 4
	TE	Resolian[a]	LLOQ (200 ng/mL) LQC (500 ng/mL) MQC (1500 ng/mL) HQC (7500 ng/mL) ULOQ (10 000 ng/mL)	13.1% 10.9% 8.8% 11.4% 24.6%	LGC327456QB10, Table 55
		[redacted]	LLOQ LQC (600 ng/mL) MQC (2000 ng/mL) HQC (4500 ng/mL) ULOQ	NA 14.2% 10.0% 18.8% NA	8471-441 addendum 01, Table 4
Cross-validation	90 incurred samples	All concentrations (n=89, 1 sample in ECLIA was BLQ)	Average difference of −26.0%; 70 (78.7%) incurred samples within ±30% difference		ARGX-PTBA-0674, Table 4, Table 5, Table 6, and Table 7
		Excluding 2 extreme observations (n=87)	Average difference of −26.1%; 70 (80.5%) incurred samples within ±30% difference		ARGX-PTBA-0674, Table 4, Table 5, Table 6, and Table 7
	11 cross-validation QC samples	11 QCs spiked with range of 600 to 40 000 ng/mL Resolian[a] ([redacted] accuracy: 87.3% to 110.3% [redacted] (ECLIA): accuracy 73.8% to 92.0% (4 out of 11 did not meet criteria) % difference [redacted] vs ECLIA: −22.9% to −9.9%			ARGX-PTBA-0674, Table 3

BLQ=below limit of quantification; CV=coefficient of variation; ECLIA=electrochemiluminescence immunoassay; HQC=high quality control; LLOQ=lower limit of quantification; LQC=low quality control; MQC=mid quality control; NA=not applicable; PK=pharmacokinetics; QC=quality control; SH=Shanghai; TE=total error; ULOQ=upper limit of quantification
a Resolian was formerly known as DDS or LGC.

Pharmacodynamics

Serum total IgG concentrations were measured to assess the PD effect of efgartigimod PH20 SC.

The REDACTED immunoturbidimetric assay kit for measuring total IgG in serum on a REDACTED platform was validated by PPD GCL-US, PPD Shanghai, and PPD Suzhou, according to the requirements of the Clinical Laboratory Improvement Amendments and the College of American Pathologists. This *in vitro* diagnostic test was further validated for drug interference and parallelism in sera from patients with CIDP. The assay at PPD GCL-US was used to analyze samples in ARGX-113-1802 and ARGX-113-1902. The methods validated at PPD Shanghai and PPD Suzhou were used to measure total IgG in participants from mainland China in ARGX-113-1802 and ARGX-113-1902.

An interlaboratory comparison study was performed between PPD Shanghai and PPD GCL-US (and between PPD Suzhou and PPD Shanghai to demonstrate that the PD method is comparable across the 3 laboratories.

Immunogenicity

The immunogenicity of efgartigimod and rHuPH20 was assessed in ARGX-113-1802 and ARGX-113-1902 using baseline and postbaseline serum or plasma samples, respectively.

A 3-tiered testing approach was used to screen, confirm, and characterize antidrug antibodies (ADA) against efgartigimod and antibodies against rHuPH20:

1. All samples were analyzed in a screening ADA assay.
2. Screened positive samples were analyzed in a confirmatory ADA assay to assess the specificity of the ADA response.
3. Confirmed positive samples were analyzed in a semiquantitative titration assay.

Confirmed positive samples were further analysed for neutralizing activity in an neutralizing antibody(ies) (NAb) assay. NAb against rHuPH20 were initially evaluated using a screening assay followed by titer analysis (i.e., a 2-tiered approach). An additional NAb confirmatory assay was implemented as a *post hoc* analysis to determine the specificity of the response (i.e., a 3-tiered approach).

Immunogenicity of Efgartigimod

An affinity capture elution (ACE) bridging enzyme-linked immunosorbent assay (ELISA) was used to measure ADA against efgartigimod in serum samples from ARGX-113-1802 and ARGX-113-1902.

This assay was validated at Resolian (formerly DDS or LGC), and supplemental validations were performed to introduce new labelled reagents. Selectivity was assessed in sera from Japanese individuals and sera from participants with CIDP.

The same method was validated at REDACTEDand used to measure ADA against efgartigimod in participants from mainland China in ARGX-113-1802 and ARGX-113-1902.

Cross-validation was performed at Resolian and REDACTED. The Applicant also completed an internal cross-comparison of the method performance at both laboratory sites. These assessments established that the ADA methods are comparable across the 2 laboratories.

Assay to Detect Neutralizing Antibodies Against Efgartigimod

All confirmed positive samples for ADA against efgartigimod were analysed for NAb activity using an indirect competition ECLIA method, including a biotin-drug extraction with acid dissociation (BEAD) pretreatment to improve the drug tolerance characteristics of the assay. While efgartigimod inhibits the interaction between FcRn and wild-type human SULFO-TAG labelled REDACTED, NAb against efgartigimod restores the assay signal. The increase in the assay signal observed in the NAb assay is directly proportional to the neutralizing potential of the antibodies. The assay is a suitable *in vitro* model to monitor the primary mechanism of action of efgartigimod, which is enhancing the reduction of endogenous IgG by outcompeting IgGs for binding to human FcRn.

The assay used to measure NAb in serum samples from ARGX-113-1802 and ARGX-113-1902 was validated at Resolian, and selectivity was assessed in sera from patients with CIDP. A supplemental validation was performed to determine selectivity in sera from Japanese individuals.

The same method was validated at REDACTEDand was used to measure NAb against efgartigimod in participants from mainland China in ARGX-113-1802 and ARGX-113-1902.

Immunogenicity of rHuPH20

Halozyme Inc (Halozyme) developed an electrochemiluminescence-based bridging immunoassay to detect antibodies against rHuPH20.

This assay was validated by REDACTED. A supplemental validation was performed to assess drug interference and selectivity in plasma from patients with CIDP. An additional validation was performed to update the system suitability limits and the long-term stability specification. This method was used to analyse samples from ARGX-113-1802 and ARGX-113-1902.

The same method was validated at REDACTEDand used to measure antibodies against rHuPH20 in participants from mainland China in ARGX-113-1802 and ARGX-113-1902.

Cross-validation was performed at REDACTEDand REDACTED. The cross-validation established that the immunogenicity methods are comparable across the 2 laboratories.

Assay to Detect Neutralizing Antibodies Against rHuPH20

All samples confirmed positive for antibodies against rHuPH20 were analysed for NAb activity using a Halozyme proprietary assay. The assay was designed to detect the presence of NAb in human plasma that can interfere with rHuPH20 activity to digest hyaluronate. Samples demonstrating neutralizing activity above the assay cut point were initially reported as positive and subjected to additional analysis to determine the endpoint NAb titer (2-tiered approach; screening and titration).

A description of the NAb assay used in ARGX-113-1802 and ARGX-113-1902 was already provided in the gMG SC submission.

The Halozyme proprietary assay was used for sample analysis in ARGX-113-1802 and ARGX-113-1902. This assay was validated at REDACTED. A supplemental validation was performed to assess drug interference and selectivity in plasma from patients with CIDP.

The same method was validated at REDACTEDand used to measure NAb activity in participants from mainland China in ARGX-113-1802 and ARGX 113-1902.

Cross-validation was performed at REDACTEDand REDACTEDto establish that results can be compared across the 2 laboratories.

The incidence of NAb against rHuPH20 in ARGX-113-1802 Stage B was 46.8% in the efgartigimod PH20 SC arm, which was higher than expected based on clinical experience with rHuPH2014 and efgartigimod PH20 SC; therefore, an additional NAb confirmatory assay was implemented post hoc as part of a 3-tiered approach (screening, confirmatory, titer analysis) to investigate these results. Screen-positive samples in the NAb against rHuPH20 assay were further evaluated in the rHuPH20 NAb confirmatory assay to determine the specificity of the response. The confirmatory assay is an immuno-depletion step using immunoglobulin-specific recombinant proteins conjugated to magnetic beads to deplete anti-rHuPH20 NAb.

The rHuPH20 NAb confirmatory method was validated at REDACTED and REDACTED. Selectivity was assessed in plasma from patients with CIDP.

Immunogenicity (Summary of Clinical Pharmacology)

Following continuous once-weekly administration of efgartigimod PH20 SC in ARGX-113-1802, the incidences of antibodies against rHuPH20 were 14.2% and 46.8% in Stage A and Stage B, respectively. No confirmed-positive NAb against rHuPh20 samples were reported in ARGX-113-1802; therefore, the

incidence of NAb against rHuPH20 was 0%. After full confirmatory analysis, the samples that were screened positive, were considered false positives due to low titers. There was no impact of antibodies against rHuPH20 on efgartigimod PK, PD, efficacy, and safety.

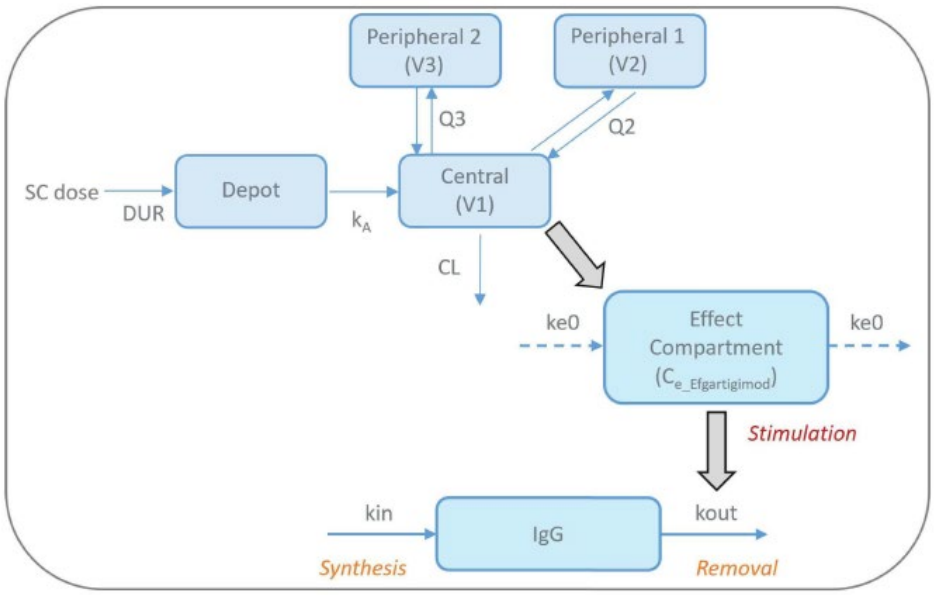
2.3.3. Pharmacokinetics

Evaluation and qualification of models

The population PK/PD modelling was performed by means of non-linear mixed-effects modelling.

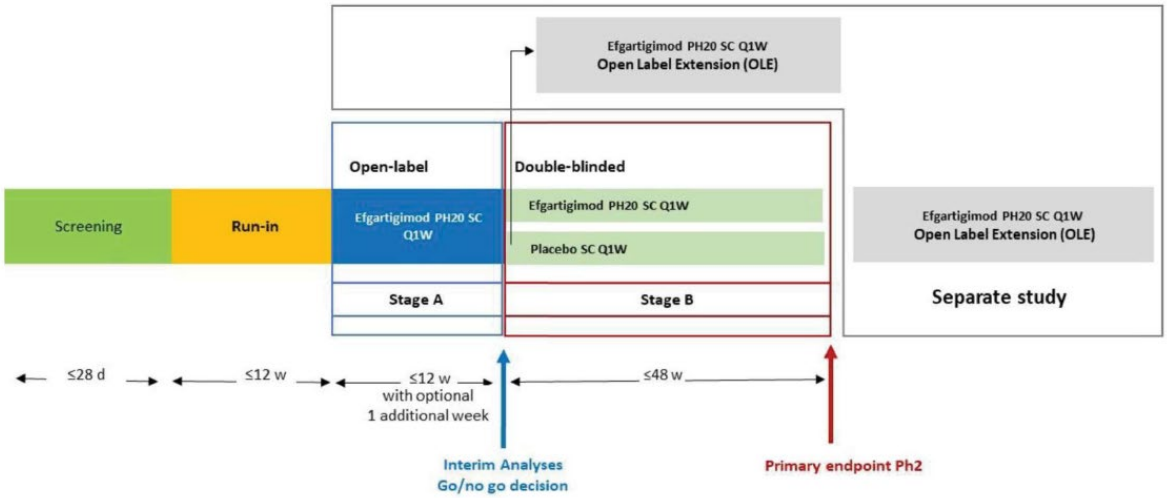
The full 3-compartment PK and PD (total IgG concentrations and reduction) models obtained with the combined analysis of efgartigimod IV and efgartigimod PH20 SC administration in healthy participants and participants with gMG was used to develop a model for patients with CIDP. The structure of the combined PK/PD model is shown in Figure 1.

Figure 1: Schematic representation of the PK model and indirect response turnover model, in which effect compartment concentration of efgartigimod stimulates the degradation rate of total IgG.



Study ARGX-113-1802 was a 2-stage study in patients with CIDP. Stage A enrolled all participants who received Q1W treatment with 1000 mg efgartigimod PH20 SC for up to 12 weeks whereas Stage B was double-blinded and placebo-controlled with randomisation in a 1:1 ratio to efgartigimod PH20 SC or placebo for patients who experienced clinical improvement in Stage A. The criteria for entering Stage B was defined as evidence of clinical improvement (ECI) at 2 consecutive visits. Pre-dose PK/PD samples were taken every week at Stage A and every 4 weeks at Stage B.

Figure 2: Study schematic for ARGX-113-1802



d = day; efgartigimod PH20 SC = efgartigimod with rHuPH20 (co-formulation) for SC administration; OLE=open-label extension ; placebo= placebo with rHuPH20; QlW = once a week; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous(ly); qlw=once weekly; w = week. Note: Participants with CIDP who showed ECI only at the last visit of the 12-weeks Stage A period could 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 participants with CIDP with confirmed ECI were randomized and received double-blind IMP in Stage B.

Pop PK model

Of the 233 participants with CIDP included in the pre-DBL PK data set from Study ARGX-113-1802 used for model development, 60 had data from Stage A only and 173 rolled over to Stage B (of which 86 received placebo and 87 received efgartigimod). The pre-DBL PK data set had 617 (20.4%) missing observations and 540 (17.8%) BLQ observations (232 pre-dose, 308 post-dose).

In the final dataset after DBL, the number of participants with CIDP increased to 332 of which 316 contributed data to the PK analysis with 2686 (73%) observations. Of note, 817 (22.2%) PK observations were BLQ (322 pre-dose, 495 post-dose) and excluded. The majority of post-dose BLQ observations came from subjects that received placebo in Stage B (Table 4).

Table 4: Overview of the excluded number of subjects and PK observations for the final PK model for study ARGX-113-1802 (final dataset)

	ARGX-113-1802	
Description	NSub	NObs
Observation records in dataset[a]	332	3678 (100%)
Missing date and clock time of observation (C=2)	1	98 (2.66%)
Missing observations (OFLAG=1)[b]	0[d]	75 (2.04%)
Below LLOQ observations (OFLAG=2)	15	817 (22.2%)[c]
Pre-dose observation PK >LLOQ before start of the first dose (OFLAG=6)	0[d]	2 (0.05%)
Included in analysis	316[e]	2686 (73.0%)

a The dataset also included dose records (EVID=I) and observation records for other (PD) endpoints. The printed Nsub and Nobs only refer to (subjects with) PK observation records
b Observations that were missing, not reported or not done and therefore not available in the input dataset
c Of these, 312 observations were pre-dose samples before the first dose, leaving 505 post-dose BLQ observations (13.7%)
d No subjects were excluded because they have other valid observations within the profile
• The number of subjects included in the analysis deviates from the number of subjects from the model output. This is caused by subjects that did not receive treatment and had no PK observations. NONMEM includes these subjects in the output files. This discrepancy had no impact on the modeling results as the number of observations was equal.

Model development was done on concentration at the end of a dosing interval (C_{trough}) data from study ARGX-113-1802 in participants with CIDP from the pre-DBL dataset that included about 70% of the final data. Prior information was used from the full covariate PK model in healthy participants and participants with gMG for all parameters except for clearance (CL), Inter-Individual Variability (IIV) on CL and

covariate effects on CL. IIV was included for CL, central volume (V1), peripheral volume of distribution V2/V3 and Absorption rate constant (Ka). Covariates not relevant for participants with CIDP were excluded. The model parameters were optimized with the bioavailability fixed to 0.765. In addition, the long and short zero-order duration from the absorption model (DUR-pop=1 and DUR-pop=2) and the fraction of participants with either short or long duration (Fraction subjects with DUR-pop=1) were fixed. The effect of albumin on CL was removed as it was not statistically significant for CIDP patients. The PK and subsequent PD response was compared across the different subject types (healthy volunteers, patients with CIDP or gMG) using Bayesian feedback and suggested that the PK of participants with CIDP was more similar to healthy participants. Hence the effects of gMG were removed on CL and V1. Further covariates were tested using a backward deletion procedure based on Δobjective function value ($p < 0.001$): bioanalytical PK assay (in the PK model) and race and ethnicity (in both PK and total IgG models). The covariate effects in the final PK model for CIDP were body weight on CL, V1, and V2/V3, estimated glomerular filtration rate (eGFR) on CL, sex on V1 and bioanalytical PK assay effect on IPRED. When the assay effect was included, 7 outliers using CWRES>6 were identified and excluded during the remaining covariate analysis. The outliers were later re-introduced and kept in the final model as they did not affect parameter estimates except for the residual error.

An overview of the parameter estimates of the final Pop PK model (G.mod) is shown in Table 5.

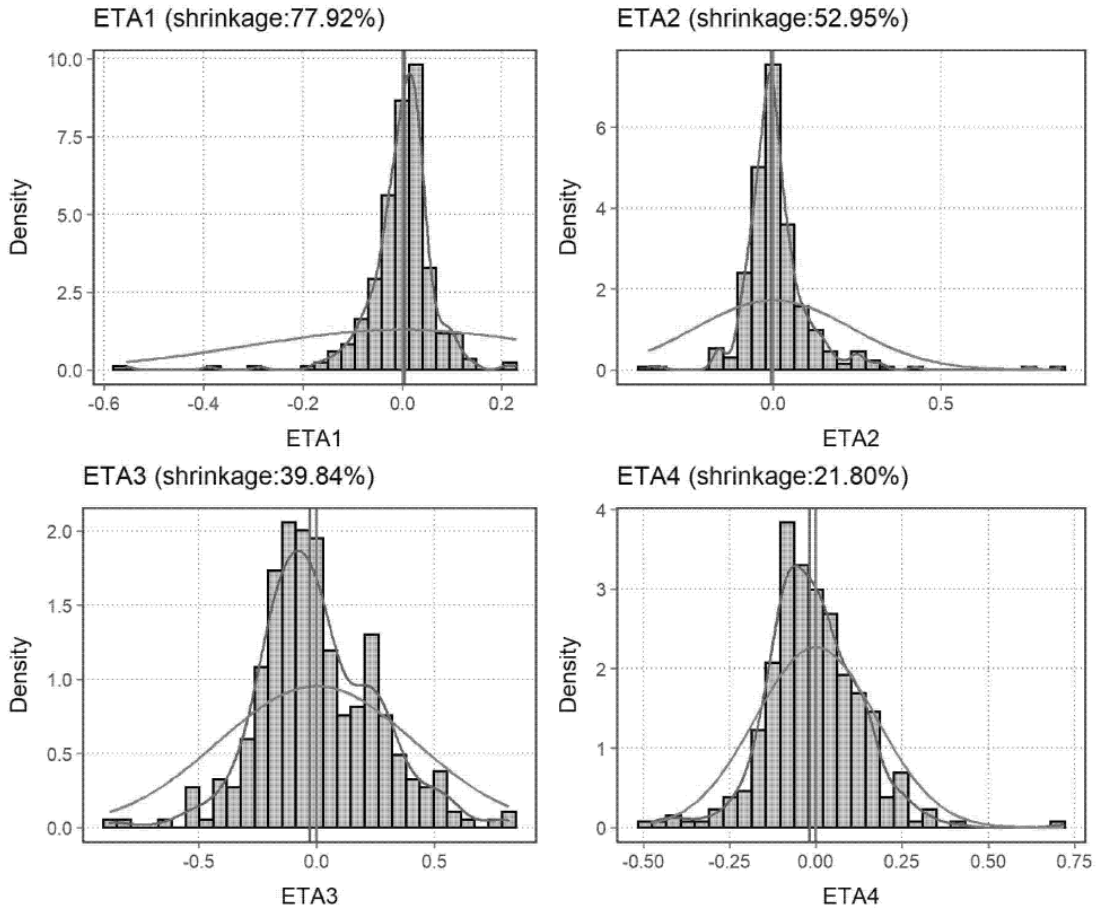
Table 5: Parameter estimates of the final PK model

Parameter [unit]	Estimate	SE	95% CI[a]	RSE (%)[b]	CV (%)[c]
Structural, Θ					
Clearance, CL (L/h)	0.134	0.002 53	(0.129, 0.139)	1.9	–
Central volume, V1 (L)	4.22	0.0913	(4.04, 4.39)	2.2	–
Intercomp clearance 1, Q2 (L/h)	0.003 41	1.58×10^{-4}	(0.00310, 0.00372)	4.6	–
Peripheral volume, V2=V3 (L)	6.69	0.132	(6.43, 6.94)	2.0	–
Intercomp clearance 2, Q3 (L/h)	0.202	0.0105	(0.182, 0.223)	5.2	–
Absorption rate, KA (1/h)	0.0201	6.96×10^{-4}	(0.0188, 0.0215)	3.5	–
Bioavailability, F6	0.765 FIX [d]	-	-	-	-
Zero-order duration, DUR-pop=1 (h)	17.4 FIX [e]	-	-	-	-
Zero-order duration, DUR-pop=2 (h)	4.05 FIX [e]	-	-	-	-
Fraction subjects with DUR-pop=1	0.467 FIX [e]	-	-	-	-
Weight effect on CL	0.721	0.0681	(0.588, 0.855)	9.4	–
eGFR effect on CL	0.585	0.0820	(0.424, 0.745)	14	–
Weight effect on V1	0.264	0.0841	(0.0994, 0.429)	32	–
Weight effect on V2	0.590	0.0703	(0.452, 0.728)	12	–
Sex effect on V1	0.767	0.0357	(0.697, 0.837)	4.7	–
Bioassay factor	0.820	0.0455	(0.731, 0.909)	5.5	–
Inter-Individual Variability, Ω					
ω^2 CL	0.0309	0.004 56	(0.0220, 0.0399)	15	17.7
ω^2 V1	0.0958	0.0341	(0.0290, 0.163)	36	31.7
ω^2 V2/V3	0.0538	0.008 44	(0.0373, 0.0704)	16	23.5
ω^2 KA	0.175	0.0227	(0.131, 0.219)	13	43.7
Residual Error, Σ					
σ^2 add. error (on log scale)	0.302	0.005 53	(0.291, 0.313)	1.8	–

a Interval calculated as 0±<ll(l-a/2) ·se(0); b RSE (%) calculated as llOO ·se(0)/0I; c CV for random effects calculated as 10OJexp(w2) - 1 and for proportional residual error as *100a* d Value taken from final PK model e Value taken from full covariate PK model (model E.mod)

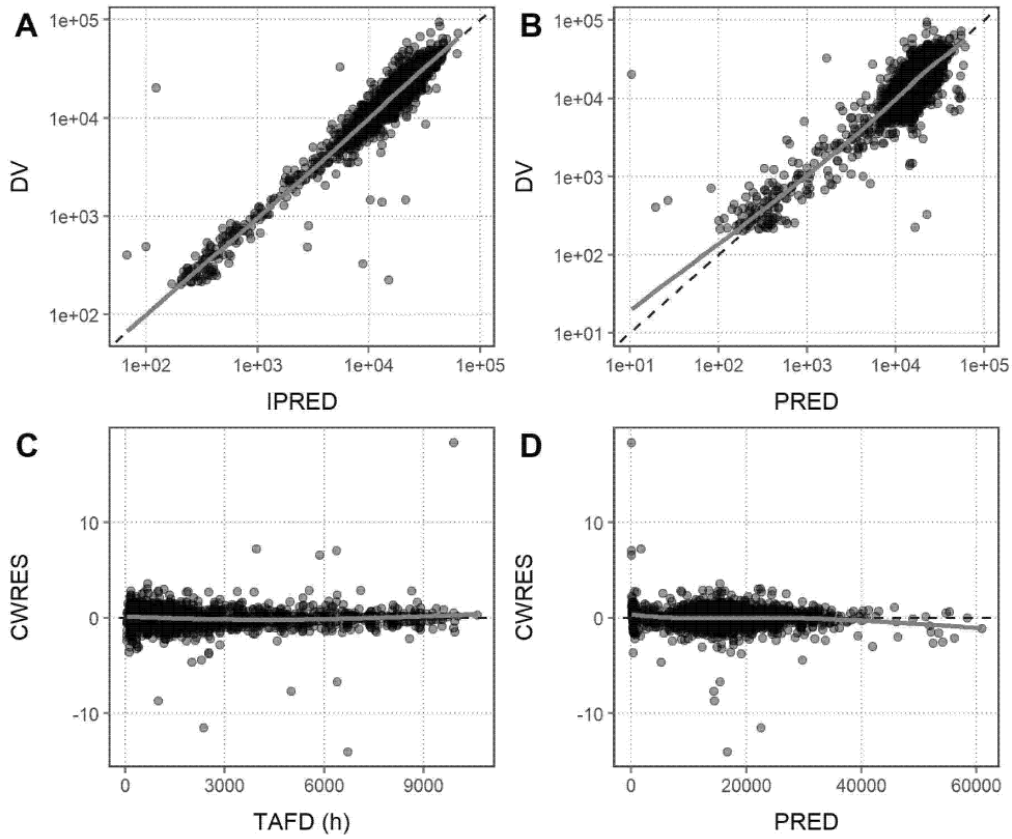
All parameters of the final PK model were estimated with RSE% values below 32% and 36% for all structural and random effects parameters, respectively. The η -shrinkage for the random effect parameters based on the final data was in the same range as the shrinkage based on the pre-DBL transfer data (Figure 3). GoF plots and VPCs are displayed in Figure 4 and Figure 5. The final PK model was used to derive the metrics area under the concentration-time curve over a dosing interval at steady state (AUC_{ss}) maximum observed serum concentration at steady-state ($C_{max,ss}$) and trough concentrations at steady-state ($C_{trough,ss}$) for all participants with CIDP based on the final dataset.

Figure 3: Shrinkage plot of IIV parameters on CL, Vl, V2/V3 and Ka for the final PK model (G.mod) (final data, after DBL).



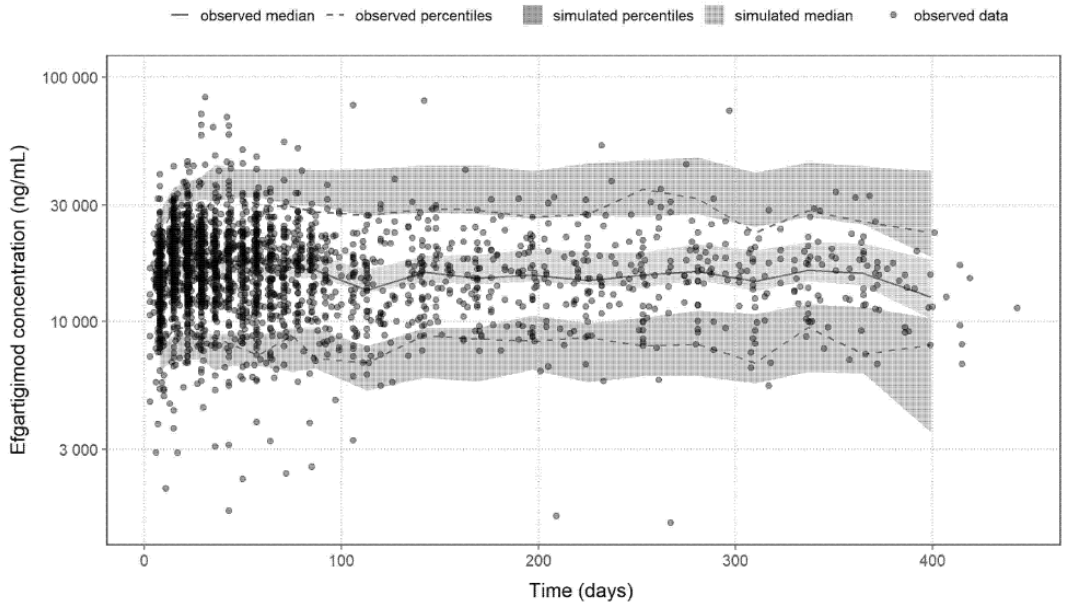
ETAl: IIV on Vl; ETA2: IIV on V2=V3; ETA3: IIV on KA; ETA4: IIV on CL Gray bars: Histogram of individual *rJ* estimates. Red line: Predicted density (curve) and median (vertical). Blue line: Observed density (curve) and median (vertical).

Figure 4: Goodness of fit plots of PK data from ARGX-113-1802 (final data, after DBL) using the final PK model (G.mod).



A: Observations *versus* individual predictions (IPRED). B: Observations *versus* population predictions (PRED). C: Conditional weighted residuals (CWRES) *versus* time after first dose (in hours). D: Conditional weighted residuals (CWRES) *versus* population fitted values. Red line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating O (C and D). DV, PRED and IPRED are plotted in ng/ml.

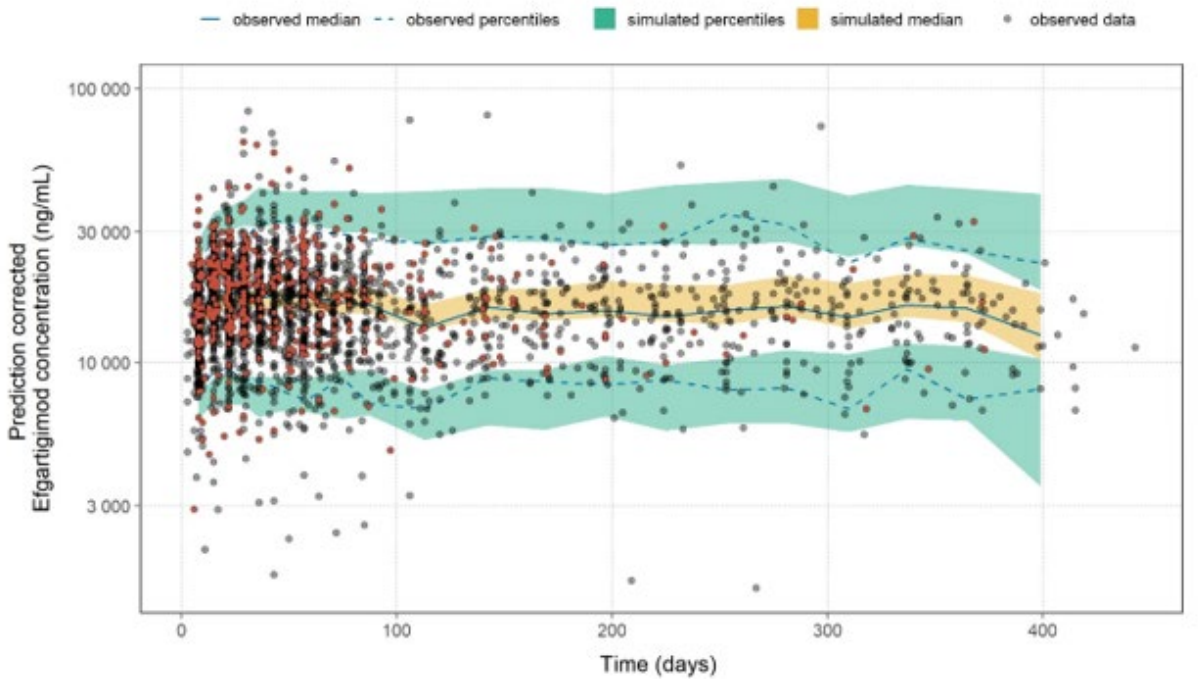
Figure 5: Prediction-Corrected Visual Predictive Checks: efgartigimod PK in ARGX-113-1802 (final data, after DBL), obtained with the final PK model (G.mod).



Gray dots: observations; *Blue solid line:* observed median; *Blue dashed lines:* percentiles of observations; *Yellow area:* confidence interval for the predicted median; *Green areas:* confidence intervals for the upper and lower percentiles of the prediction interval. Simulation results are shown for a prediction interval of 90% (5th-95th percentile). Confidence intervals represent a confidence level of 95%.

The prediction corrected visual predictive check (pcVPC) of efgartigimod PK in ARGX-113-1802, including color coding for samples measured with the ECLIA (red dots) and the sandwich immunoassay method (gray dots), is presented in Figure 6.

Figure 6: Prediction-Corrected Visual Predictive Checks of efgartigimod PH20 serum concentrations from participants with CIDP in study ARGX-113-1802 (final data, final PK model)



CIDP= chronic inflammatory demyelinating polyneuropathy; ECLIA=electrochemiluminescence immunoassay; PK= pharmacokinetic(s).
The red dots represent prediction corrected efgartigimod concentrations in samples measured with the ECLIA (samples from participants from mainland China). The gray dots represent prediction corrected efgartigimod concentrations from samples measuresd with the sandwich immunoassay method (samples from all other participants). The solid blue line is the prediction corrected observed median. The dashed blue lines are percentiles of prediction-corrected observations. The yellow area shows the Cis for the predicted median. The green areas show the Cis for the upper and lower percentiles of the prediction interval. Simulation results are shown for a prediction interval of 90% (5^{th}-95^{th} percentile). CIs represent a confidence interval of 95%.

PK/total IgG model

In the final PD data set, 322 participants contributed 3419 total IgG observations (Table 6).

Table 6: Overview of the excluded number of subjects and total lgG observations for the final PK/total lgG model for study ARGX-113-1802 (final dataset)

	ARGX-113-1802	
Description	N_{sub}	N_{obs}(%)
Observation records in dataset	341	4146 (100%)
Screening and run-in observations (PER=0)	19	331 (7.98%)
Missing observations (OFLAG=1)	0[a]	116 (2.8%)
Double total lgG records	0[a]	215 (5.19%)
Double total lgG records with OFLAG=13	0[a]	1 (0.02%)
Included in analysis	322	3419 (82.5%)

a No subjects were excluded because they have other valid observations within the profile
b The number of subjects included in the analysis deviates from the model output. This is caused by subjects that only had total lgG observations during the screening period . NONMEM includes these subjects in the output files. This discrepancy had no impact on the modeling results as the number of observations was equal.

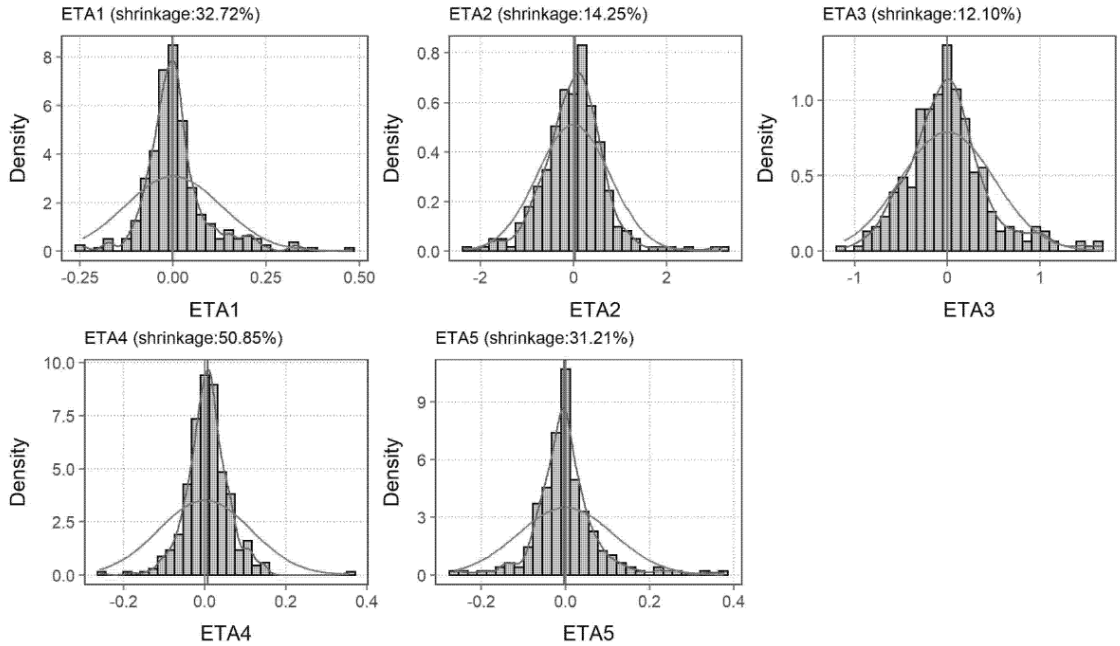
The full covariate PD model developed for healthy participants and participants with gMG was used as a starting point. Omitting gMG patient effects on degradation Rate constant (kout) and concentration at half-maximal effective concentration (EC_{50}) resulted significantly improved the objective function value, hence these effects were removed. All parameters in the gMG PK/total IgG model, except maximal reduction from baseline/maximal effect (E_{max}) which was fixed to the 4.97, were re-estimated based on the total IgG data in participants with CIDP. Six outliers (CWRES >6) were identified and excluded at this stage. The CIDP-relevant covariates identified during the forward inclusion for healthy participants and participants with gMG were tested for significance in participants with CIDP: Alkaline phosphatase (ALP) and race on baseline total IgG, Aspartate aminotransferase (AST) on kout, and weight on EC_{50}. All four effects were removed during a step-wise backward deletion. Additional covariate effects related to ethnicity and race were not significant. To better capture the variability of observations, the observed Stage A total IgG baseline was added as a covariate effect for the total IgG baseline parameter. In addition, Inter-Occasion Variability was implemented on the total IgG baseline to describe the variability between Stage A and Stage B. As IIV on delay rate constant (Keo) could not be identified, IIV was included for BL, EC50 and kout. The OMEGA BLOCK in NONMEM was used to handle significant correlation between the random effects. As a last step identified outliers were reintroduced and kept in the final PK/total IgG model as they did not influence the parameter estimates (Table 7, Figure 7,Figure 8, Figure 9, Figure 10).

Table 7: Comparison of parameter estimates between the existing final PK/total IgG model (M .tIgG .mod) 12 and the final PK/total IgG model in participants with CIDP (I.mod)

Parameter Name	**Estimate (95% CI) - M.tIgG.mod***	**Estimate (95% CI) - I.mod**	**Rel. diff** (%)**
Baseline, BL (ug/mL)	8727 (8415, 9038)	11871 (12828, 13557)	36.0
Elimination rate, k_{out} (1/h)	0.00211 (0.00196, 0.00225)	0.00179 (0.00162, 0.00196)	-15.2
Maximum effect, E_{max} (-)	4.97 (4.63, 5.31)	4.97 FIX	-
Potency, EC_{50} (ng/mL)	39182 (35838, 42527)	30439 (26028, 34853)	-22.3
Effect compartment rate constant,k_{eo} (1/h)	0.0203 (0.0182, 0.0223)	0.0430 (0.0295, 0.0565)	111.8
Co-medication effect (corticos-teroids) on BL	0.793 (0.707. 0.880)	-	-
Baseline total IgG effect on BL	-	0.873 (0.784, 0.963)	-
Variability	**Estimate (%CV)**	**Estimate (%CV)**	
ω^2 BL	0.0885 (30.4)	0.0167 (13.0)	NA
ω covariance BLxEC_{50}	0.0422 (22.2)	0.0424 (35.6)	NA
ω^2 EC_{50}	0.205 (47.7)	0.611 (91.7)	NA
ω covariance EC_{50}xk_{out}	0.110 (53.1)	0.300 (60.6)	NA
ω^2 k_{out}	0.173 (43.5)	0.256 (54.0)	NA
ω covariance BLxk_{out}	-	0.0348 (49.6)	NA
Residual Error	**Estimate (stDev)**	**Estimate (stDev)**	
σ^2 Proportional error total IgG	0.0176 (0.133)	0.0147 (0.121)	-8.6

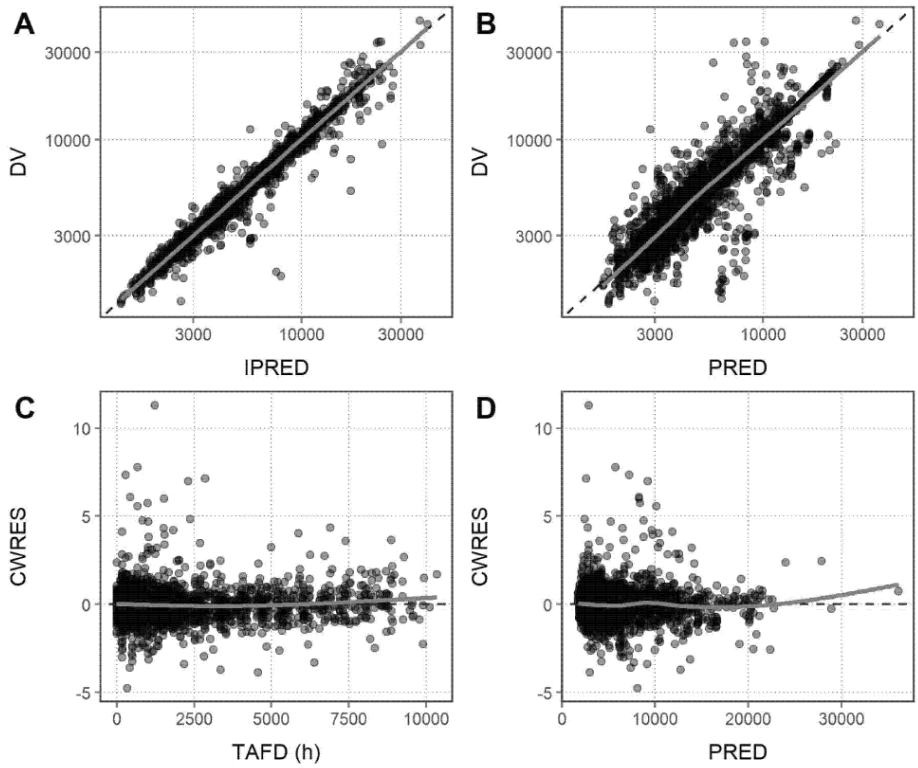
RSE (%) is calculated as SE/Estimate*lO0 ; 95% Cl is calculated as Estimate+/- 1.96*SE; %CV is calculated as sqrt(exp(w2)-1)*100 in case of an exponential model ; StDev is calculated as sqrt(error) . The correlation coefficient for the covariance element (reported in the %CV column) is calculated as 100%·(Wcovariancelx2)/(sqrt(exp(wj!) - 1) * sqrt(exp(w~) - 1)).
*This table only shows relevant parameters for comparison (parameters related to gMG patient effects are not reported here, and IIV on keo) not shown.
** Relative difference for the structural parameters was calculated based on parameter estimates. Relative difference for the variability parameters was not applicable (NA) due to the different IIV structure of both models, therefore, the values of the random effect parameters cannot be directly compared . Relative difference for the residual error was calculated based on the stDev.

Figure 7: Shrinkage plot of I IV parameters on baseline total lgG, EC50 , and kout for the final PK/total lgG model (I.mod) (final data, after DBL).



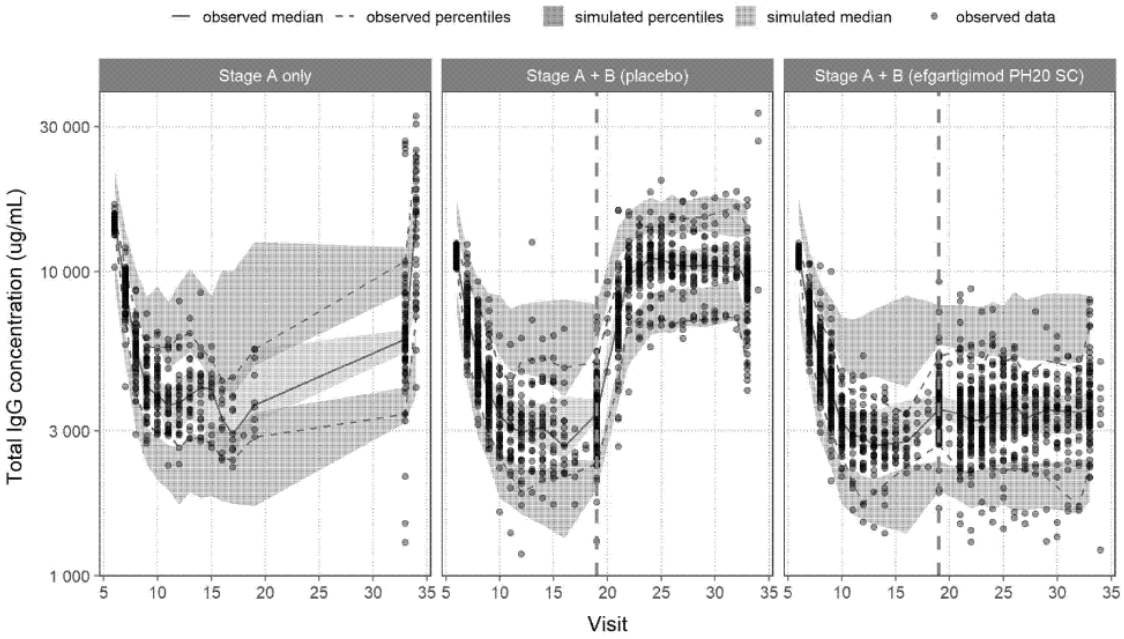
ETAl: IIV on BL-lgGt; ETA2: IIV on EC50; ETA3: IIV on kout•
Gray bars: Histogram of individual *rJ* estimates. Red line: Predicted density (curve) and median (vertical). Blue line: Observed density (curve) and median (vertical).

Figure 8: Goodness of fit plots (all data) of total lgG concentrations from all participants with CIDP in ARGX-113-1802 (pre-DBL transfer) using the final PK/total lgG model (I.mod).



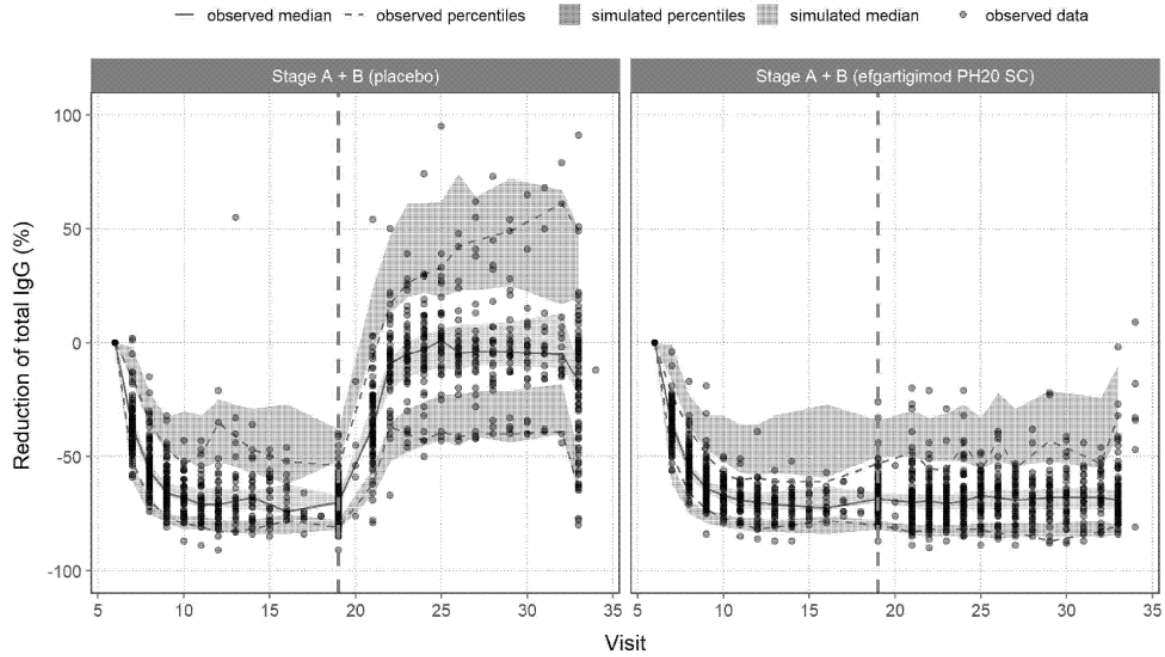
A: Observations *versus* individual predictions (IPRED). B: Observations *versus* population predictions (PRED). C: Conditional weighted residuals (CWRES) *versus* time after first dose (in hours). D: Conditional weighted residuals (CWRES) *versus* population fitted values. Red line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating O (C and D). DV, PRED and IPRED are plotted in µ.g/ml.

Figure 9: Prediction-Corrected Visual Predictive Checks: total IgG concentration in participants with CIDP receiving efgartigimod PH20 SC of study ARGX-113-1802 (final data, after DBL), stratified by stage and treatment received in Stage B, obtained with the final PK/total IgG model (I.mod).



Gray dots: observations; *Blue solid line:* observed median; *Blue dashed lines:* percentiles of observations; *Yellow area:* confidence interval for the predicted median; *Green areas:* confidence intervals for the upper and lower percentiles of the prediction interval. *Vertical dashed line:* end of Stage A. Simulation results are shown for a prediction interval of 90% (5th -95th percentile). Confidence intervals represent a confidence level of 95%. Visit refers to the numbered study visits. The 'END OF STUDY EARLY DISCONTINUATION' and 'FOLLOW-UP' visits were manually changed to visit 33 and 34, respectively-:-

Figure 10: Visual Predictive Checks: the reduction of total IgG concentration in participants with CIDP receiving efgartigimod PH20 SC of study ARGX-113-1802 (final data, after DBL), stratified by stage and treatment received in Stage B, obtained with the final PK/total IgG model (I.mod) (without participants with Stage A only).



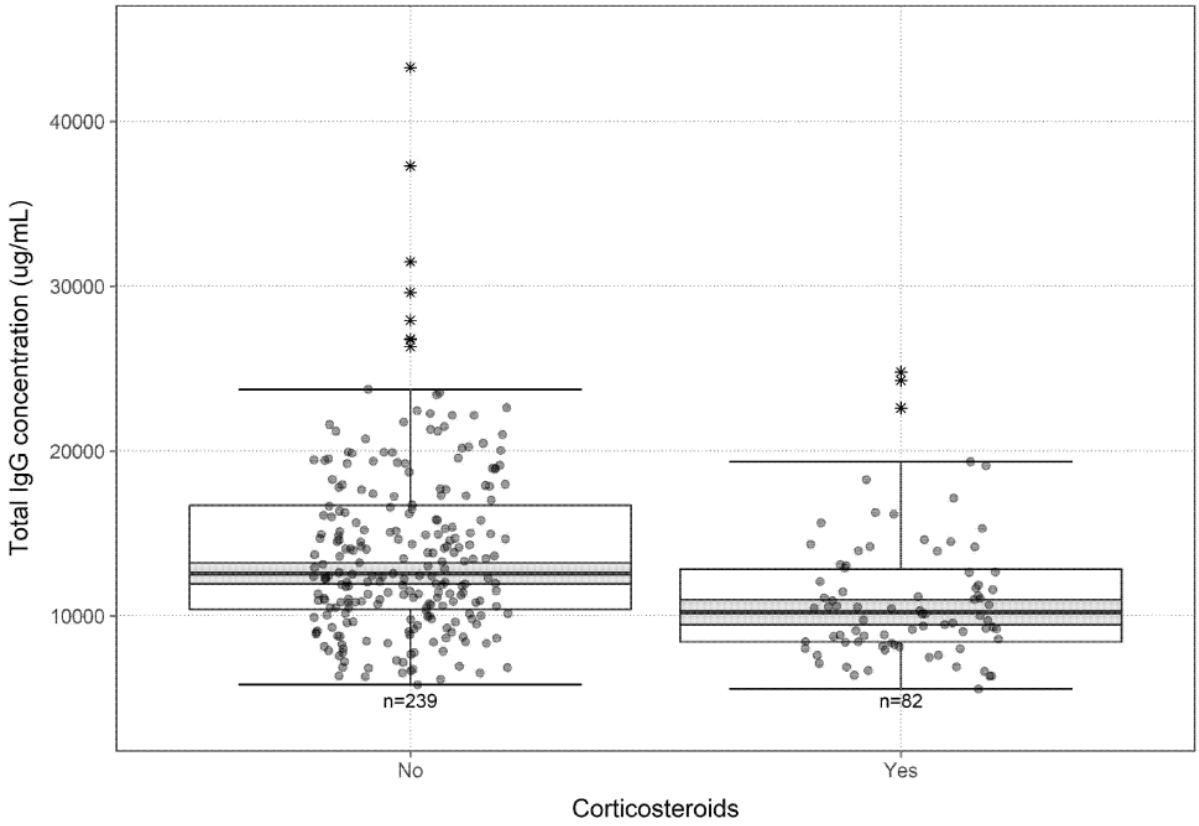
Gray dots: observations; *Blue solid line:* observed median; *Blue dashed lines:* percentiles of observations; *Yellow area:* confidence interval for the predicted median; *Green areas:* confidence intervals for the upper and lower percentiles of the prediction interval. *Vertical dashed line:* end of Stage A. Simulation results are shown for a prediction interval of 90% (5th -95th percentile). Confidence intervals represent a confidence level of 95%. Visit refers to the numbered study visits. The 'END OF STUDY EARLY DISCONTINUATION' and 'FOLLOW-UP' visits were manually changed to visit 33 and 34, respectively-:-

"Pretreated" CIDP population

The "pretreated population" is defined as participants who received CIDP therapy (IVIg, SCIg, and/or corticosteroids) within 6 months before screening in study ARGX-113-1802 and with a CIDP Disease Activity Status (CDAS) score ≥4 at screening.

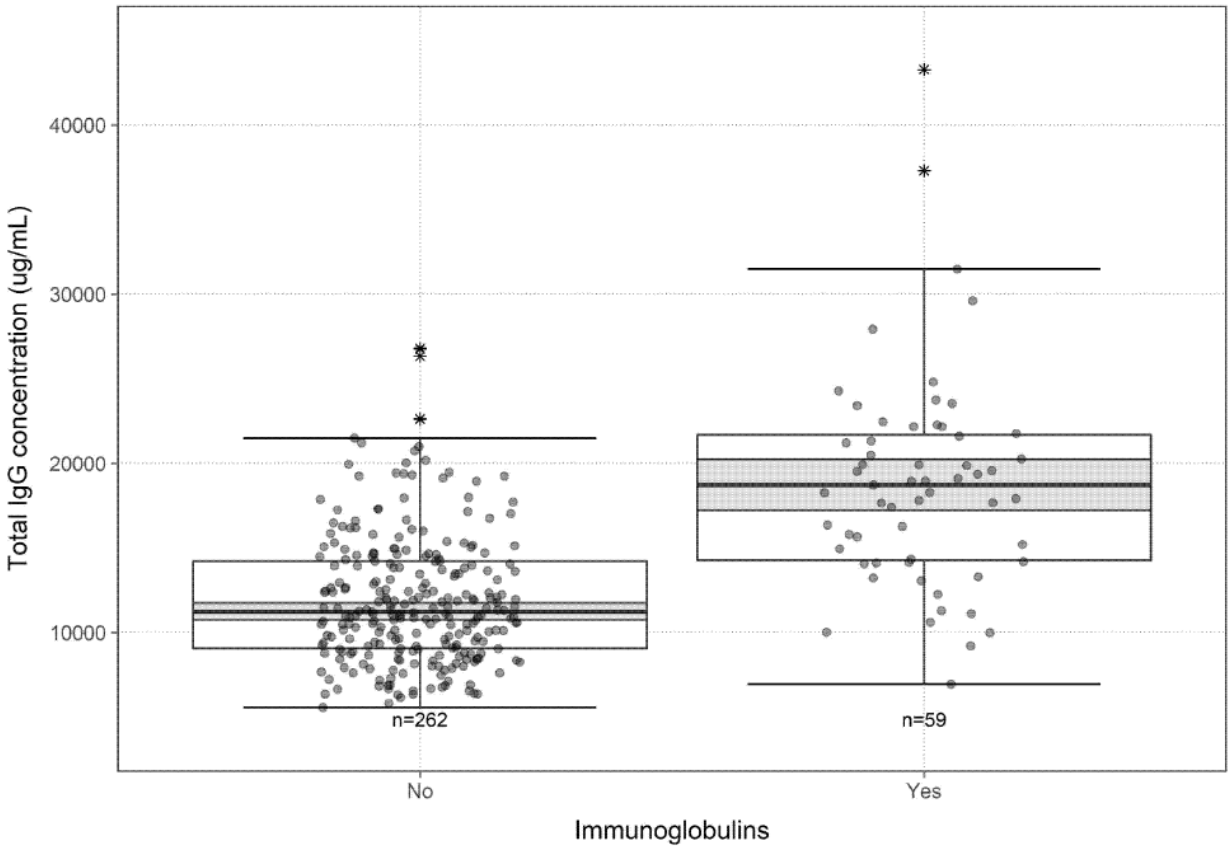
Of note, co-medication information was only available in the final dataset and not in the pre-DBL data set, used for model development. An exploratory analysis was initially performed on use of prior corticosteroids and immunoglobulins. The effect of prior CIDP medication on Stage A baseline total IgG is shown in Figure 11 and Figure 12, for corticosteroids and immunoglobulin, respectively.

Figure 11: Relationship between prior corticosteroids use and model-predicted Stage A baseline total IgG (final data, after DBL) based on the final PK/total IgG model (I.mod).



Whiskers (Black bars): Range between the lowest prediction still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest prediction still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Shaded area: g5% confidence interval of the median. Black horizontal line: Median. Gray dots: individual predictions. Asterixis: Outliers (individual values outside of whiskers).

Figure 12: Relationship between prior immunoglobulins use and model-predicted Stage A baseline total IgG (final data, after DBL) based on the final PK/total IgG model (I.mod).

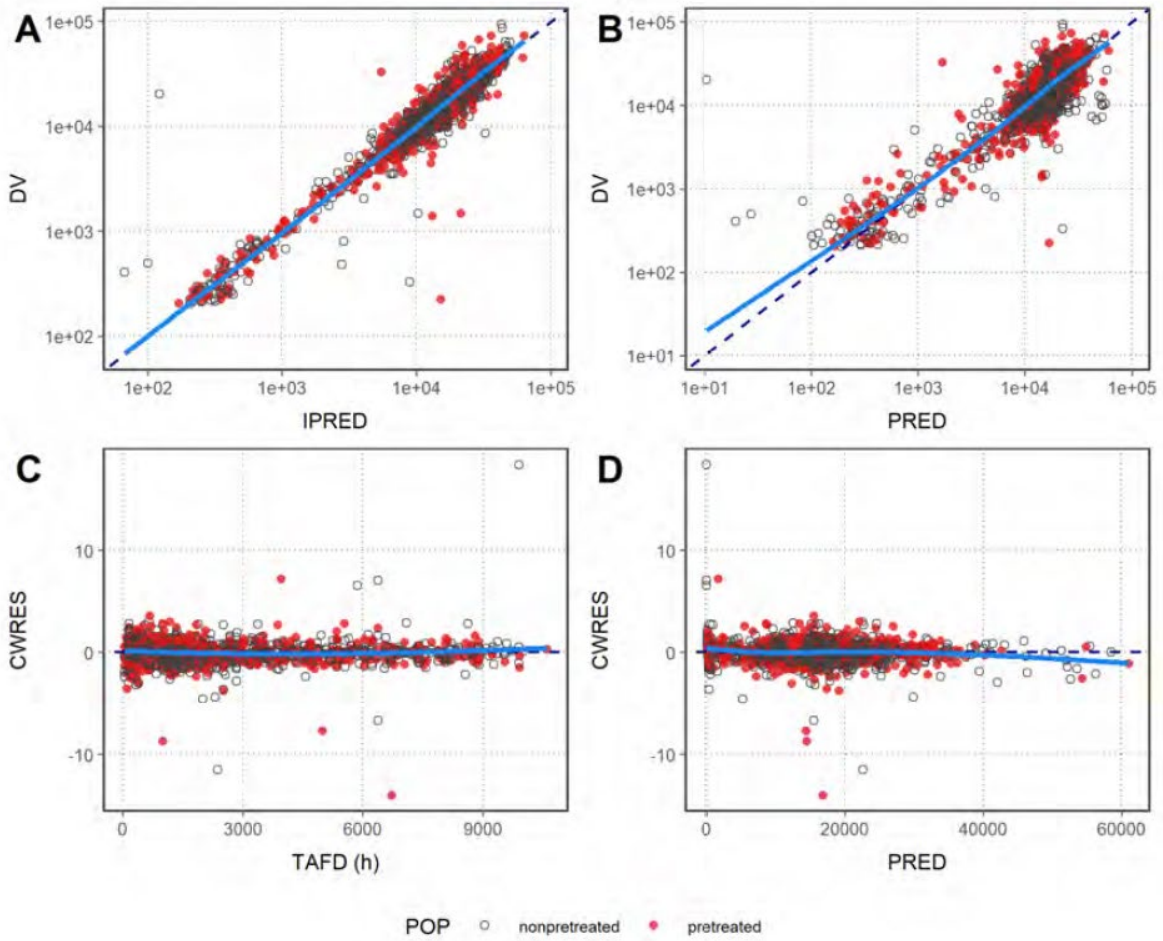


Whiskers (Black bars): Range between the lowest prediction still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest prediction still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Shaded area: g5% confidence interval of the median. Black horizontal line: Median. Gray dots: individual predictions. Asterixis: Outliers (individual values outside of whiskers).

To support an indication in the EU for pretreated patients, the final PK and PK/total IgG models were used in a simulation study to investigate potential similarities/differences in efgartigimod exposure between pretreated and overall populations of participants with CIDP.

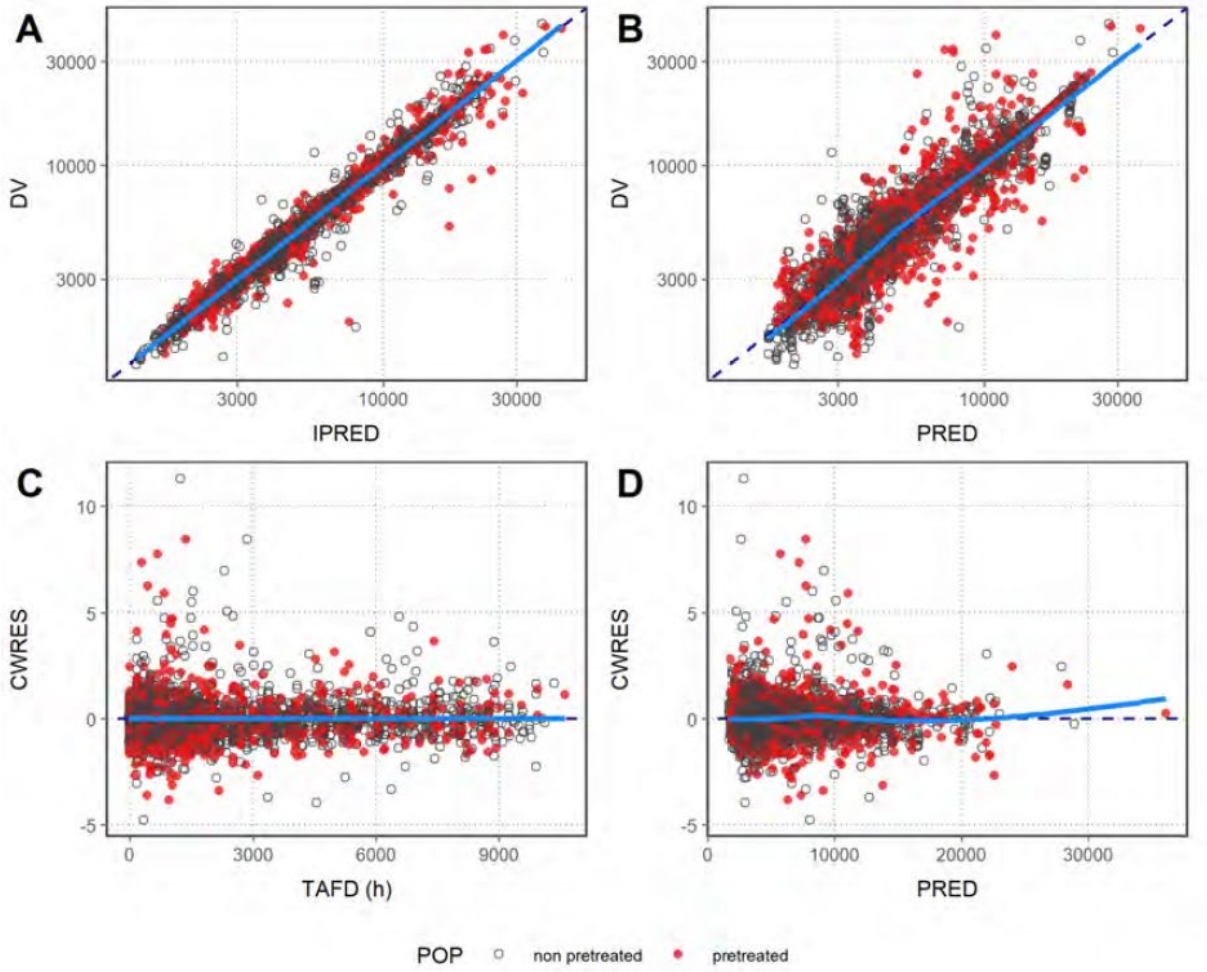
The final models were used without any modifications to predict exposure metrics at steady state for the pretreated and overall populations of participants with CIDP who received efgartigimod PH20 SC treatment in study ARGX-113-1802, as well as the area under the effect curve at steady-state ($AUEC_{ss}$), the maximum, trough, and average total IgG reduction in Stage A of the pretreated population versus the overall population of participants. To ensure steady-state, 24 weekly doses of 1000 mg efgartigimod PH20 SC were simulated for each participant. Figure 13 and Figure 14 show GoF plots of the PK and IgG data in pretreated and non-pretreated patients.

Figure 13: Goodness of fit plots of PK data in the pretreated and overall populations of participants with CIDP from ARG-113-1802 using the final PK model (G.mod)



A: Observations *versus* individual predictions (IPRED). B: Observations *versus* population predictions (PRED). C: Conditional weighted residuals (CWRES) *versus* time after first dose (TAFD) (in hours). D: Conditional weighted residuals (CWRES) *versus* population fitted values. Blue line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating 0 (C and D). Red dots: pretreated population. Open circles: overall population. DV, PRED and IPRED are plotted in ng/mL.

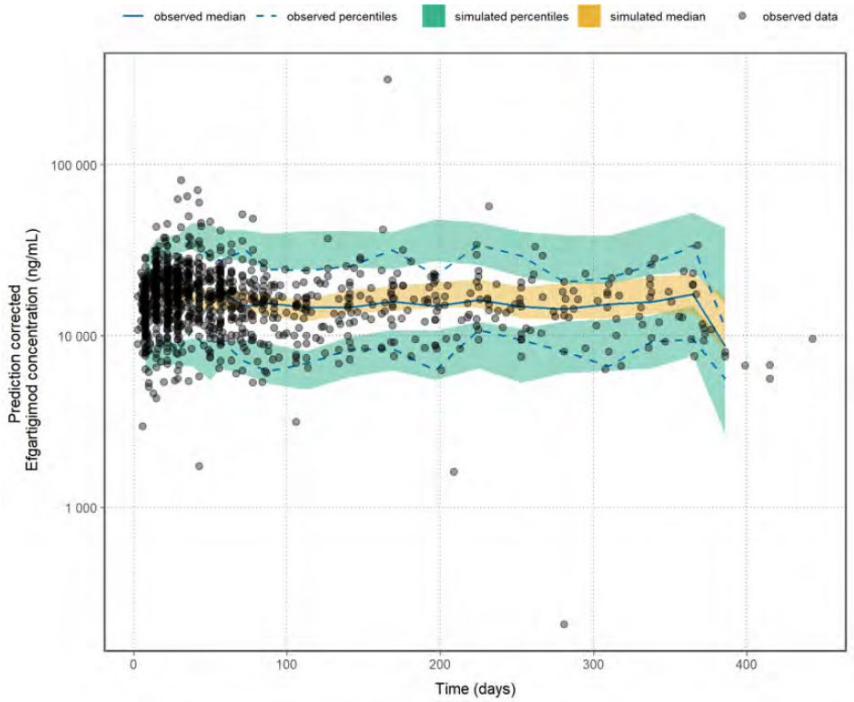
Figure 14: Goodness of fit plots of total IgG data in the pretreated and overall populations of participants with CIDP from ARG-113-1802 using the final PK model (G.mod)



A: Observations *versus* individual predictions (IPRED). B: Observations *versus* population predictions (PRED). C: Conditional weighted residuals (CWRES) *versus* time after first dose (TAFD) (in hours). D: Conditional weighted residuals (CWRES) *versus* population fitted values. Blue line: Loess smooth through data. Dashed line: line of identity (A and B) or line indicating 0 (C and D). Red dots: pretreated population. Open circles: overall population. DV, PRED and IPRED are plotted in ng/mL.

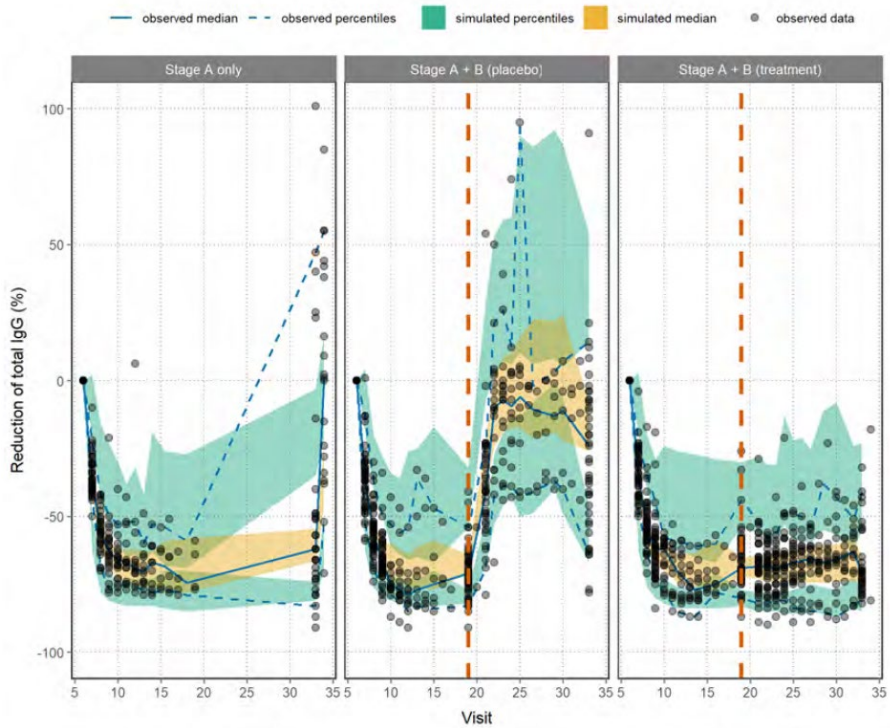
For the patient subpopulation defined as pretreated, Figure 15 show a pcVPC of PK data and Figure 16 show a VPC of Total IgG reduction across the different study stages of ARGX-113-1802.

Figure 15: Prediction-Corrected Visual Predictive Checks: efgartigimod PK in the pretreated population of participants with CIDP receiving efgartigimod PH20 SC in ARGX-113-1802, obtained with the final PK model (G.mod).



Gray dots: observations; *blue solid line*: observed median; *blue dashed lines*: 5th and 95th percentiles of observations; *yellow area*: 90% confidence interval for the predicted median; *green areas*: 90% confidence interval for the 5th and 95th percentiles of the prediction interval

Figure 16: Visual Predictive Checks: the reduction of total IgG concentrations in the pretreated population of participants with CIDP receiving efgartigimod PH20 SC in ARGX-113-1802, obtained with the final PK/total IgG model (I.mod).

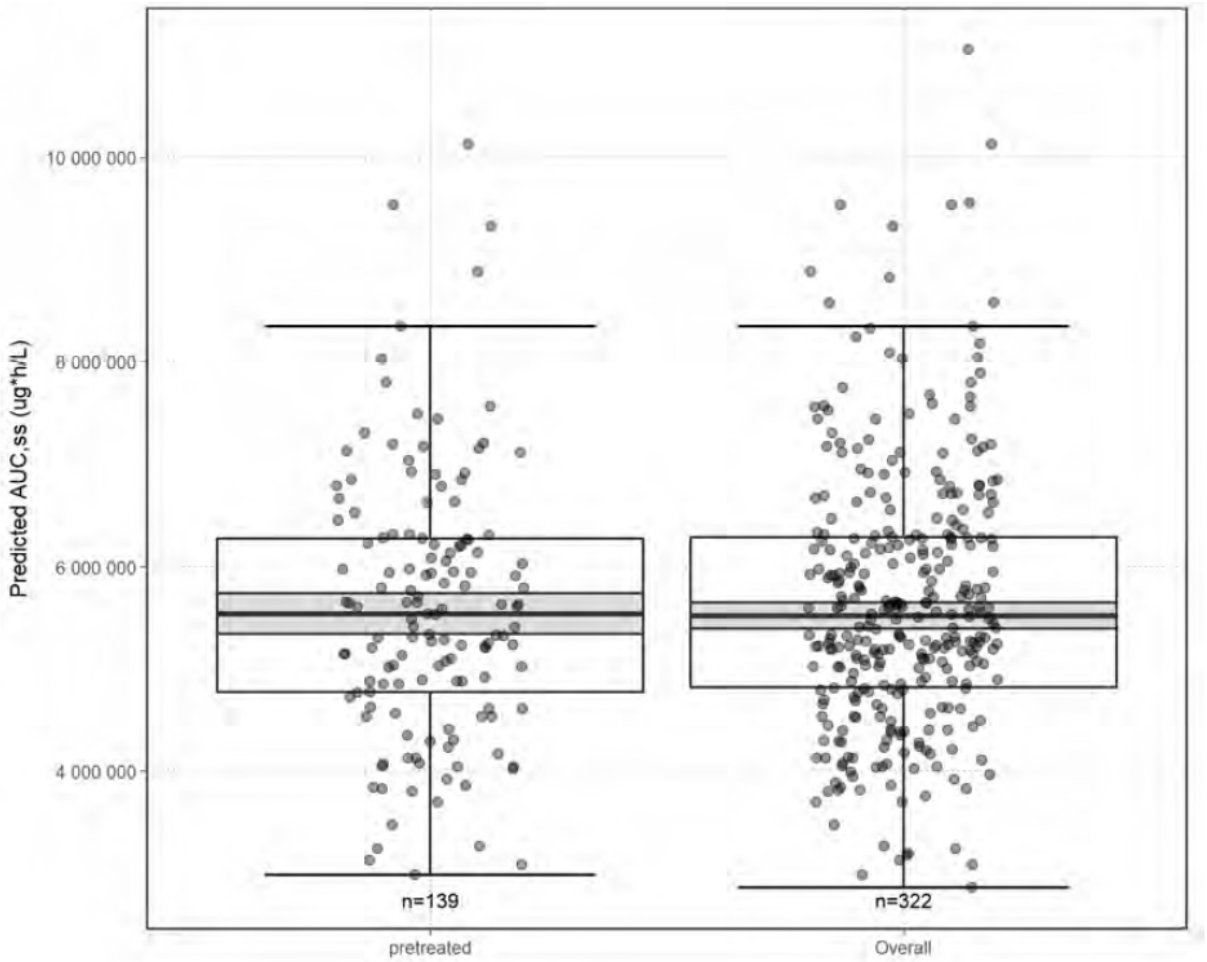


Gray dots: observations; *Blue solid line*: observed median; *Blue dashed lines*: percentiles of observations; *Yellow area*: confidence interval for the predicted median; *Green areas*: confidence intervals for the upper and lower percentiles of the prediction interval. *Vertical dashed line*: end of Stage A. Simulation results are shown for a prediction interval of 90% (5th-95th percentile). Confidence

intervals represent a confidence level of 95%. Visit refers to the numbered study visits. The 'END_OF_STUDY_EARLY_DISCONTINUATION' and 'FOLLOW-UP' visits were manually changed to visit 33 and 34, respectively.

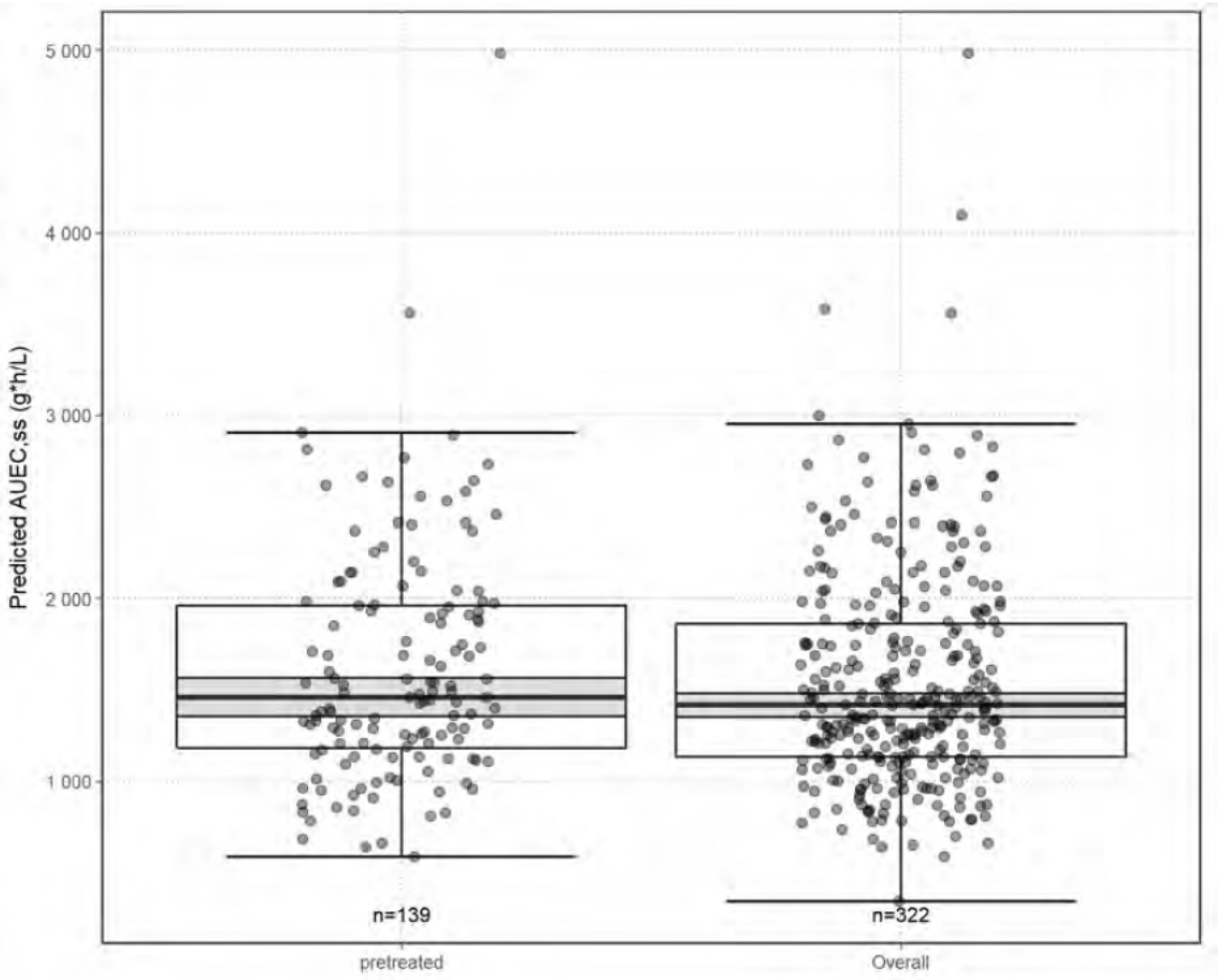
Figure 17 and Figure 18 compare predicted AUC and AUEC at steady state, respectively, of pretreated and overall populations of participants with CIDP who received efgartigimod PH20 SC treatment.

Figure 17: Distribution of the predicted AUCss of the pretreated and overall populations of participants with CIDP who received efgartigimod PH20 SC treatment in ARGX-113-1802, using the final PK model (G.mod).



Whiskers (Black bars): Range between the lowest observation still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest observation still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Box width reflects number of observations. Notches: 95% confidence interval of the median. Black horizontal line: Median. Gray dots: Individual observations.

Figure 18: Distribution of the predicted AUECss of pretreated and overall populations of participants with CIDP who received efgartigimod PH20 SC treatment in ARGX-113-1802, using the final PK/total IgG model (I.mod).



Whiskers (Black bars): Range between the lowest observation still within 1.5 x the interquartile range (IQR) of the lower quartile and the highest observation still within 1.5 x interquartile range (IQR) of the upper quartile. Box: Range between lower and upper quartile. Box width reflects number of observations. Notches: 95% confidence interval of the median. Black horizontal line: Median. Gray dots: Individual observations.

Pharmacokinetics (studies)

Pharmacokinetics of Efgartigimod in Participants With CIDP:

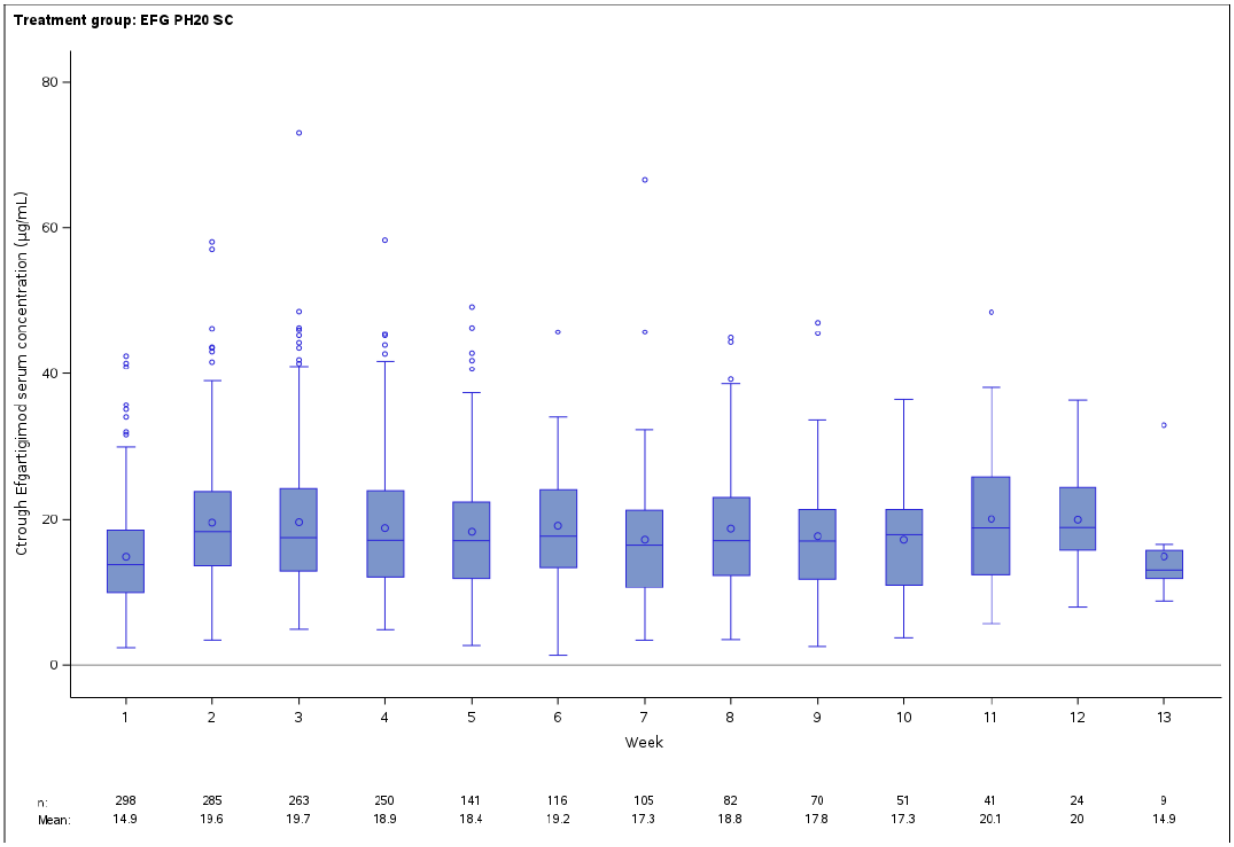
ARGX-113-1802 (Overall Population)

A boxplot of Ctrough every week (Stage A) or every 4 weeks (Stage B) during once-weekly administrations of efgartigimod PH20 SC 1000 mg is presented in Figure 19 and Figure 20, respectively.

Efgartigimod mean (SD) Ctrough remained stable from 2 weeks after the first efgartigimod PH20 SC administration throughout the total treatment period of 60 weeks of Stage A and Stage B (efgartigimod PH20 SC arm), with values ranging from 14.9 (7.24) to 20.1 (9.64) µg/mL. In participants who entered the Stage B placebo arm, the mean (SD) efgartigimod serum concentrations decreased to 0.267 (0.365) µg/mL within 4 weeks and to levels below the limit of quantification (0.200 µg/mL) after that.

The mean (SD) efgartigimod serum concentrations at 48 to 96 hours (around Cmax) after the first (n=12) and fourth (n=11) efgartigimod PH20 SC administration, collected in a subset of Japanese participants, were 23.2 (10.3) and 42.5 (14.1) µg/mL, respectively

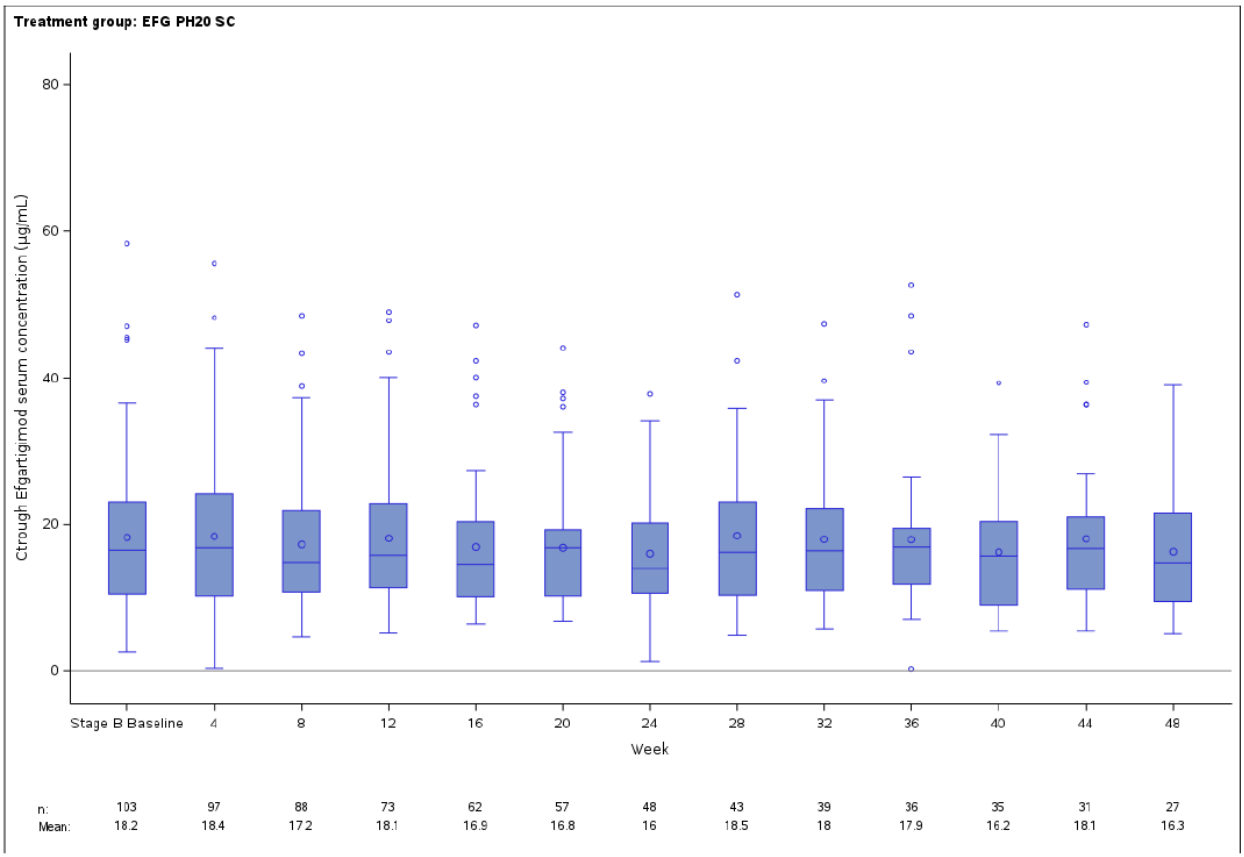
Figure 19: Study ARGX-113-1802, Stage A: Efgartigimod Ctrough Over Time After Once-Weekly Administrations of Efgartigimod PH20 SC in Participants With CIDP (Overall Population)



CIDP=chronic inflammatory demyelinating polyneuropathy; CSR=clinical study report; Ctrough=observed concentration at the end of a dosing interval immediately before administration of next dose; EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IQR=interquartile range; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Notes: The solid line is the median. The large O indicates the mean, and the small o indicates the outliers. The ends of the boxplot are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5x IQR of the lower quartile and the highest value still within 1.5x IQR of the upper quartile

Figure 20: Study ARGX-113-1802, Stage B: Efgartigimod Ctrough Over Time After Once-Weekly Administrations of Efgartigimod PH20 SC in Participants With CIDP (Overall Population)



CIDP=chronic inflammatory demyelinating polyneuropathy; CSR=clinical study report; Ctrough=observed concentration immediately before administration of next dose; EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IQR=interquartile range; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The solid line is the median. The large O indicates the mean, and the small o indicates the outliers. The ends of the boxplot are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5x IQR of the lower quartile and the highest value still within 1.5x IQR of the upper quartile.

ARGX-113-1902 (Interim Analysis (IA) 1)

The PK evaluation of ARGX-113-1902 is based on interim data (data cutoff date 14 Apr 2023). A boxplot of C_{trough} during once-weekly efgartigimod PH20 SC 1000 mg show similar serum concentrations as in the 1802 study.

Efgartigimod mean (SD) C_{trough} remained stable throughout the study, with values between 16.8 (9.75) and 19.4 (9.58) µg/mL.

Dose proportionality and time dependencies

Dose Proportionality

The dose proportionality of efgartigimod PH20 SC was discussed in the gMG SC submission. No evidence of deviation from dose proportionality was observed for efgartigimod C_{max} and area under the concentration-time curve from zero to infinite time ($AUC_{0\text{-}inf}$) within the 750 to 1750 mg dose range (comixed with rHuPH20) upon single dosing.

Accumulation and Time Dependency

The accumulation and time dependency of efgartigimod PH20 SC after 4 once-weekly administrations were discussed in the gMG SC submission. Also, in participants with CIDP, the accumulation of efgartigimod PH20 SC was limited, with Ctrough remaining stable over the entire treatment duration in ARGX-113-1802 and ARGX-113-1902.

Dose Justification

The recommended dose of efgartigimod PH20 SC for patients with CIDP is 1000 mg, administered once weekly.

Increasing evidence suggests that IgG autoantibodies play a key role in CIDP. Therefore, the selected dose and dosing regimen of efgartigimod PH20 SC in ARGX-113-1802 targeted a near-maximal PD effect (i.e., reduction of pathogenic IgGs). The dose of 1000 mg efgartigimod PH20 SC was based on previous studies in healthy participants and participants with gMG.

Administration of 4 weekly doses of efgartigimod IV 10 mg/kg was shown to provide close-to-maximum total IgG reduction with higher dose levels not resulting in significant differences in total IgG reduction (gMG IV submission). Four weekly doses with efgartigimod PH20 SC 1000 mg resulted in a similar total IgG reduction as that with efgartigimod IV 10 mg/kg based on the results from ARGX-113-2001 (participants with gMG) and ARGX-113-1907 (healthy participants) (gMG SC submission,).

Population PK/PD modelling further justified the use of a fixed dose of 1000 mg of efgartigimod PH20 SC (gMG SC submission).

A continuous dosing regimen to maintain the suppression of pathogenic IgGs was considered appropriate for a disease such as CIDP with a persistent autoimmune mechanism. A once-weekly dosing regimen was shown to consistently maintain total IgG levels close to maximal suppression associated with favourable clinical efficacy outcomes. Furthermore, the safety and efficacy profile of efgartigimod PH20 SC 1000 mg was established in the approved gMG indication.

The results of ARGX-113-1802 demonstrated that continuous once-weekly administration of efgartigimod PH20 SC 1000 mg resulted in similar total IgG reductions in participants with CIDP as compared with healthy participants and participants with gMG, confirming that the targeted near-maximal PD effect was achieved. The rapid, consistent, and sustained total IgG reductions coincided with favourable clinical efficacy outcomes as well as a favourable safety and tolerability profile in participants with CIDP . In Stage A of ARGX-113-1802, treatment with once-weekly efgartigimod PH20 SC 1000 mg resulted in a reduction in total IgG levels during the first 4 weeks when maximal reduction occurred. This reduction coincided with a rapid onset of clinical effect. Participants treated with efgartigimod PH20 SC in Stage B had sustained total IgG reductions, maintained a clinical response, and remained relapse-free longer than participants who received placebo and whose total IgG levels had returned to baseline within 8 weeks after treatment withdrawal. Moreover, no differences in the time to clinical deterioration across quartiles of total IgG reduction and efgartigimod exposure were observed. Also, no increasing trend in the frequency of AEs or adverse event of special interest (AESIs) with higher exposure to efgartigimod or increased total IgG reduction was identified.

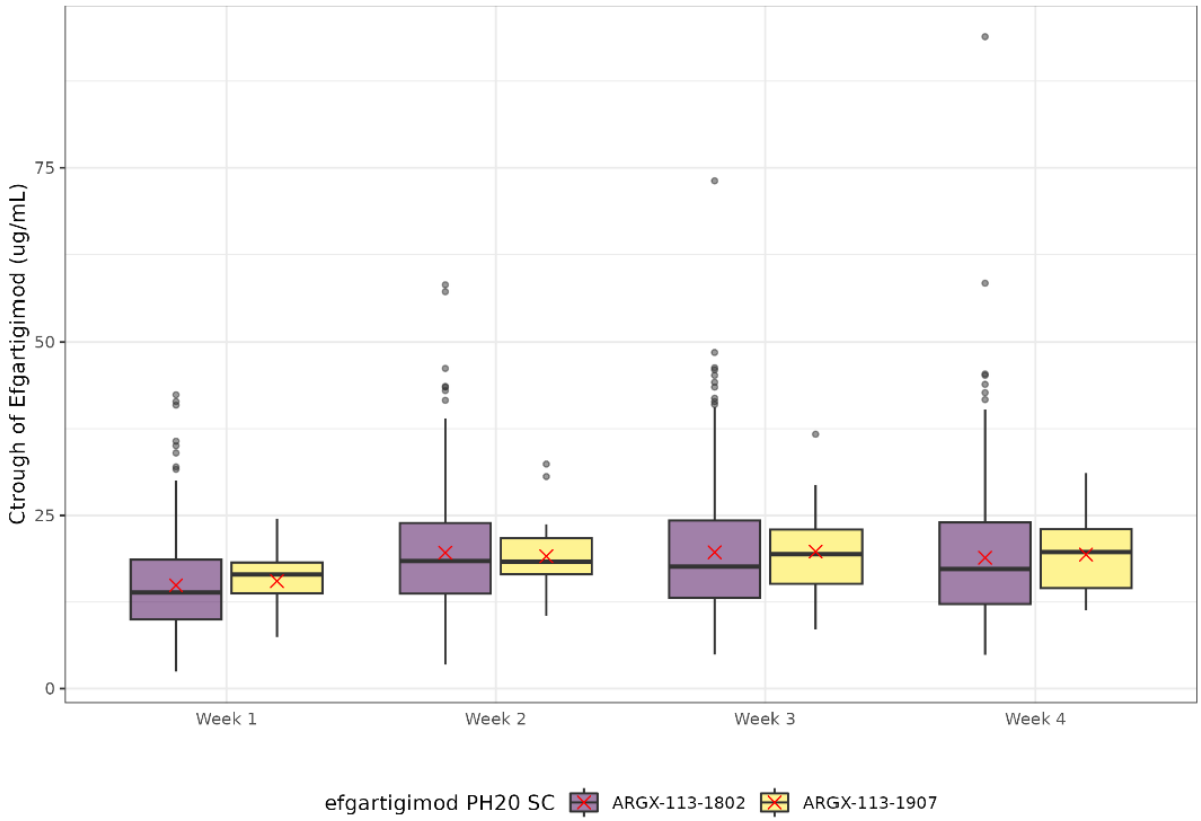
In summary, a continuous once-weekly dosing regimen of efgartigimod PH20 SC 1000 mg is considered an appropriate dosing regimen in patients with CIDP. Once-every-2-weeks dosing may be considered in some patients.

Comparability Between Participants with CIDP and Healthy Participants

Pharmacokinetics

Evaluation of the PK profile of efgartigimod obtained after 4 once-weekly injections of efgartigimod PH20 SC 1000 mg indicates that the PK profile of efgartigimod is similar in participants with CIDP and in healthy participants (Figure 21).

Figure 21: Box Plot of Ctrough After 4 Once-Weekly Administrations of Efgartigimod PH20 SC 1000 mg in Participants With CIDP (Overall Population) and Healthy Participants



CIDP=chronic inflammatory demyelinating polyneuropathy; CSR=clinical study report; Ctrough=observed concentration immediately predose at weeks 1, 2, 3, and 4 after administration of efgartigimod PH20 SC 1000 mg at weeks 0, 1, 2, and 3; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IQR=interquartile range; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The solid horizontal line is the median; the red symbol is the arithmetic mean. The ends of the boxes are the 25th and 75th percentiles. The whiskers show the lowest data value within 1.5 IQR of the lower quartile and the highest value within 1.5 IQR of the upper quartile. The gray circles indicate the outliers.

Additionally, comparison between the parameter estimates of the final PK model from healthy participants and participants with gMG and the parameter estimates of the final PK model from participants with CIDP shows that CL, V1, and V2/V3 values were comparable across models (ie, <5% difference).

Intersubject variability

In the population PK analysis, statistically significant covariate effects of body weight (on CL, V1, V2/V3), eGFR (on CL), and sex (on V1) were identified. The variability of the final PK model parameters CL, V1, and V2/V3 was moderate to low (ie, 17.7%, 31.7%, and 23.5%, respectively).

The observed intersubject variability on Ctrough efgartigimod concentrations levels after once-weekly administrations of efgartigimod PH20 SC 1000 mg was moderate, with %CV over time ranging from 34.4% to 59.6% (Table 8 and Table 9).

Table 8: Table 14.2.15.1

ANALYSIS SET: STAGE A PK

TREATMENT: EFG PH20 SC

	STAGE A BASELINE		Week 1	Week 2	Week 3		Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Safety FU after Stage A
STATISTICS	0h	48-96h	0h	0h	0h	48-96h	0h	0h	0h	0h	0h	0h	0h	0h	0h	0h
n	24	12	24	24	23	11	22	9	6	5	5	4	3	3	2	4
Mean	BLQ	23.2	16.1	22.6	22.8	42.5	19.6	23.1	17.5	19.4	18.7	20.7	20.2	24.5	22.3	0.699
S.D.	NC	10.3	6.57	9.21	12.7	14.1	9.30	8.82	4.02	4.86	3.79	4.00	8.68	5.35	6.29	0.367
Min	BLQ	BLQ	7.62	10.0	7.12	14.8	6.10	12.4	10.5	15.2	14.4	16.9	10.9	18.6	17.8	0.386
Q1	BLQ	19.2	11.4	17.4	17.4	36.1	14.2	18.1	16.8	15.9	16.5	17.5	10.9	18.6	17.8	0.451
Median	BLQ	24.3	14.1	21.8	21.4	39.5	19.1	23.1	17.8	18.7	17.3	20.1	21.5	26.0	22.3	0.596
Q3	BLQ	32.3	20.5	24.8	25.5	51.9	25.1	26.6	19.1	19.6	22.6	23.9	28.1	29.0	26.7	0.948
Max	60.3	35.5	30.0	46.2	73.1	64.1	45.2	40.6	22.8	27.4	22.8	25.7	28.1	29.0	26.7	1.22
CV (%)	NC	44.4	40.7	40.8	55.8	33.3	47.6	38.2	23.0	25.1	20.2	19.3	43.0	21.8	28.3	52.5

Table 9: Table 14.2.15.3

ANALYSIS SET: STAGE B PK

TREATMENT: EFG PH20 SC (N=111)

STATISTICS	STAGE B BASELINE	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Safety FU after Stage B
n	103	97	88	73	62	57	48	43	39	36	35	31	27	6
Mean	18.2	18.4	17.2	18.1	16.9	16.8	16.0	18.5	18.0	17.9	16.2	18.1	16.3	0.831
S.D.	9.96	10.3	9.11	9.48	9.03	8.36	7.89	10.2	9.50	10.7	8.20	10.2	8.18	1.06
Min	2.63	0.327	4.62	5.13	6.46	6.82	1.38	4.83	5.81	0.224	5.52	5.53	5.04	BLQ
Q1	10.6	10.3	10.8	11.4	10.2	10.3	10.7	10.4	11.0	11.8	8.95	11.2	9.43	0.250
Median	16.5	16.8	14.9	15.8	14.6	16.8	14.1	16.2	16.4	16.9	15.7	16.7	14.8	0.546
Q3	23.1	24.2	21.9	22.9	20.4	19.3	20.2	23.1	22.1	19.5	20.4	21.0	21.5	0.714
Max	58.3	55.6	48.5	49.0	47.1	44.1	37.8	51.3	47.3	52.7	39.3	47.2	39.0	2.93
CV (%)	54.6	56.2	52.9	52.3	53.4	49.7	49.3	55.2	52.9	59.6	50.6	56.6	50.3	128

In the final population PK/total IgG model in participants with CIDP, the variability of baseline total IgG level and EC_{50} was 13.0% and 91.7%, respectively.

Special populations

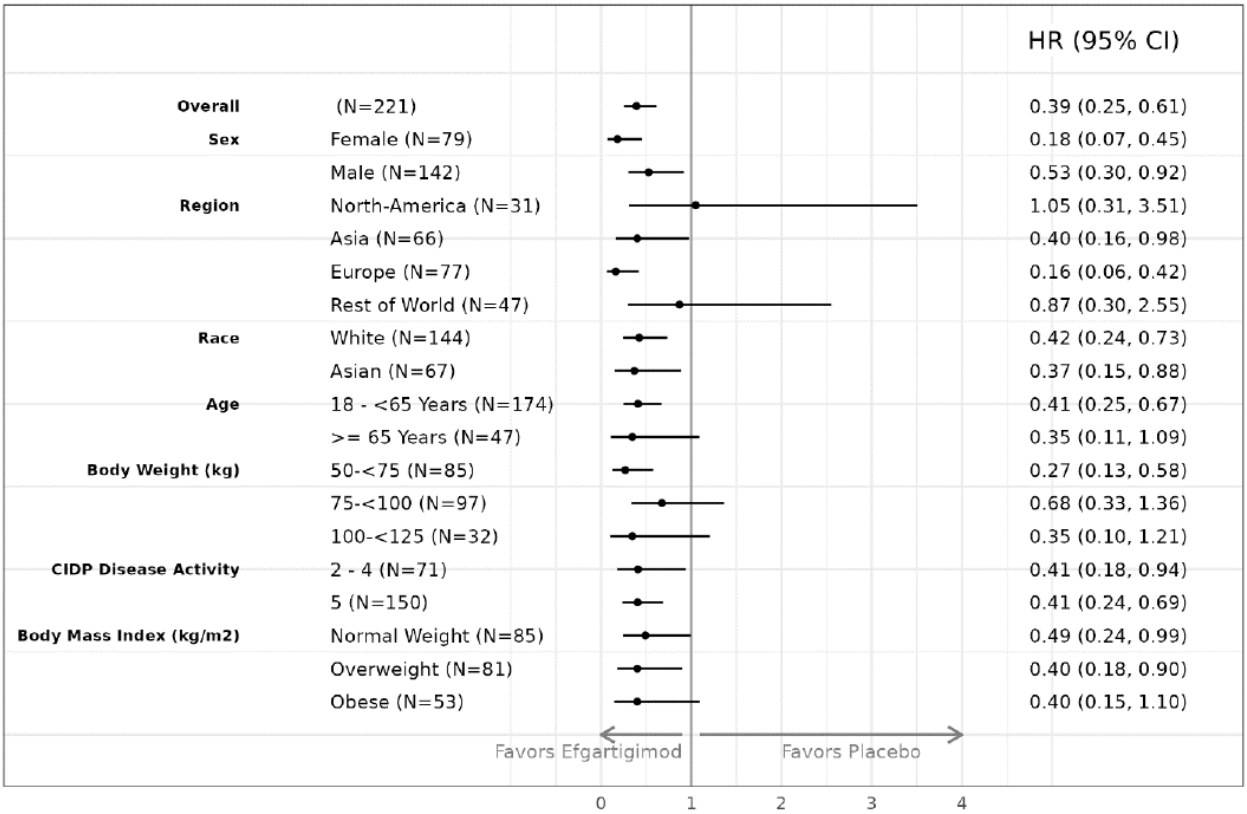
Body weight

The effect of body weight on the exposure of efgartigimod is modest and not clinically relevant.

The effect of body weight on efgartigimod PK was assessed in the population PK/total IgG analysis. Body weight was a statistically significant covariate in the final population PK model, with CL increasing and efgartigimod exposure decreasing with increasing body weight. The AUCss after once-weekly dosing of efgartigimod PH20 SC 1000 mg was simulated for a participant from ARGX-113-1802 with the 5th or 95th percentile body weight and compared to a reference participant with a median body weight of 79.6 kg; a participant with a body weight of 52.7 kg (5th percentile) will have a relative increase in AUCss of +34.7% (90% CI: +23.9% to +46.8%); a participant with a body weight of 114.0 kg (95th percentile) will have a relative AUCss decrease of −22.8% (90% CI: −15.8% to −29.0%).

Body weight was not identified as a statistically significant covariate in the population PK/total IgG model. Also, the effect of efgartigimod PH20 SC as assessed by time to first occurrence of clinical deterioration was consistent and similar to the overall effect across different body weight categories (Figure 22).

Figure 22: Forest Plot of the Time to First Occurrence of Clinical Deterioration – HR (95% CI) Overall and by Subgroups (mITT Analysis Set) (Stage B – Primary Endpoint – Subgroup Analysis)



CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; EEA=European Economic Area; EFTA=European Free Trade Association; EU=European Union; HR=hazard ratio; mITT=modified intent-to-treat; ROW=rest of world; UK=United Kingdom; US=United States Notes: North America (US, Canada); Asia (China, Japan, Taiwan); Europe (EU, UK, EEA, EFTA countries); and ROW (including Ukraine, Russian Federation, Georgia, Israel, Serbia, Turkey)

Age

The median (min, max) age for participants with CIDP receiving efgartigimod PH20 SC in ARGX-113-1802 was 56.0 (20.0, 82.0) years in Stage A (n=322) and 56.0 (22.0, 82.0) years in Stage B (efgartigimod arm, n=111), with the majority of participants (76.7% and 77.5%, respectively) in the 18 to <65 years age category.

The assessment of the effect of age on efgartigimod PK and PD in the population PK/total IgG analysis developed for healthy participants and participants with gMG showed no influence of age on any model parameters (gMG SC submission). In line herewith, no effect of age on PK and PD was assumed for participants with CIDP.

Sex at birth

The majority of the participants receiving efgartigimod PH20 SC in ARGX-113-1802 were male (64.6% in Stage A and 65.8% in Stage B [efgartigimod PH20 SC arm]). The effect of sex on efgartigimod exposure was limited and not clinically meaningful.

A statistically significant effect of sex on V1 was identified in the population PK model . Based on the dataset of ARGX-113-1802, the median and 90% CI of the AUCss ratio for female participants compared to male participants was 1.09 (1.03-1.15). After analysis of 10 000 simulated replicates of the data set, accounting for the underlying interindividual variability and parameter uncertainty, the median, 5th percentile, and 95th percentile of the 10 000 ratios and corresponding 90% confidence intervals (Cis) were estimated to be 1.13 (1.08-1.18), 1.06 (1.02-1.11), and 1.19 (1.14-1.25), respectively. The 90% CIs of the ratios fell within the bioequivalence limits of 0.8 to 1.25, and the observed difference is not

considered clinically relevant. In addition, the slightly higher exposure in females is likely attributed to the identified body weight effect on CL.

Race and ethnicity

Of the 322 participants with CIDP receiving efgartigimod PH20 SC in ARGX-113-1802 Stage A, the most common race category was White (65.5%), followed by Asian (27.6%), Chinese (18.0%), and Japanese (7.5%). The most common ethnicity category was "not Hispanic or Latino" (89.4%). A similar distribution among the different races and ethnicities was observed in participants receiving efgartigimod PH20 SC in Stage B.

The effect of race and ethnicity on efgartigimod PK and PD was assessed in the population PK/PD analysis. Covariate effects of Chinese and Japanese participants with CIDP and other race and ethnicity categorizations on CL were not significant. Also, no significant effect of Chinese or Japanese participants with CIDP or other race categories was observed in the population PK/total IgG model.

The efgartigimod concentrations measured 48 to 96 hours (around C_{max}) after the fourth administration of efgartigimod PH20 SC in a subset of Japanese participants and were aligned with those previously measured in non-Japanese healthy participants and non-Japanese participants with gMG (gMG SC submission

Renal impairment

With a molecular weight of approximately 54 kDa, efgartigimod is at the boundary of the size of molecules that are renally filtered. A population covariate analysis was performed to evaluate the potential effect of eGFR as a marker of renal function on the PK and PD profile of efgartigimod. A statistically significant reduction in CL with decreasing renal function was identified in the population PK model, resulting in an increase of exposure. After simulation of once-weekly administration of efgartigimod PH20 SC 1000 mg, a participant with an eGFR of 76.4 mL/min/1.73 m² (5th percentile in ARGX-113-1802) was estimated to have a relative AUCss increase of +20.4% (90% CI: +12.9% to +29.1%) compared with a reference participant with CIDP with a median eGFR of 105.0 mL/min/1.73 m², and a participant with an eGFR of 137.0 mL/min/1.73 m2 (95^{th} percentile in ARGX-113-1802) was estimated to have a relative AUCss decrease of −14.4% (90% CI: −8.3% to −19.8%).

Similar results were observed in a categorical evaluation based on eGFR value. Here, participants with CIDP in ARGX113-1802 with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m2) were estimated to show a 21% (90% CI: +13% to +30%) higher AUCss, compared with participants with normal renal function (eGFR ≥90 mL/min/1.73 m2). After 10 000 simulated replicates of the data set, accounting for the underlying interindividual variability and parameter uncertainty, the median, 5th percentile, and 95th percentile of the 10 000 ratios and the corresponding 90% CIs were estimated to be 1.21 (1.14-1.27), 1.11 (1.05-1.18), and 1.31 (1.23-1.38), respectively.

The results for CIDP align with findings in earlier analyses in gMG (gMG SC submission. Mild renal impairment at baseline did not affect the overall safety profile of efgartigimod.

There were insufficient data to evaluate the effect of moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m2) and severe renal impairment (eGFR <30 mL/min/1.73 m2) on the PK of efgartigimod in participants with CIDP.

Hepatic impairment

Although allowed per study inclusion and exclusion criteria, no participants with CIDP with hepatic impairment have been enrolled. Therefore, no clinical data for patients with hepatic impairment are available. The effect of hepatic impairment on the PK and PD of efgartigimod has not been studied; however, it is unlikely to be present.

Markers of hepatic function were evaluated as potential covariates in the population PK/PD analysis. In the full covariate model, AST and ALP were identified as covariates for the PK/total IgG model for healthy participants and participants with gMG. Both were tested and were evaluated as not significant for participants with CIDP in ARGX-113-1802. The effect of albumin on CL was not statistically significant in the final population PK model for.

Pharmacokinetic interaction studies

Effect of Prior or Concomitant Medications on the PK and PD of Efgartigimod

The effect of rHuPH20 on the PK of efgartigimod is limited, and no effect of rHuPH20 on the reduction in total IgG levels was observed (gMG SC submission.

Concomitant CIDP therapy was not allowed in ARGX-113-1802.

Efgartigimod is a human IgG1 Fc fragment modified to have an increased affinity for the FcRn. Compared to the wild-type Fc fragment, efgartigimod has significantly increased affinity for human FcRn at both neutral and acidic pH (gMG IV submission). Therefore, it is not expected that therapeutic antibodies with no increased binding affinity to FcRn are able to affect the interaction of efgartigimod with the FcRn receptor and, as such, no effect of therapeutic antibodies or immunoglobulins on the PK or PD of efgartigimod is expected.

The potential effect of IVIg on efgartigimod PK has been evaluated after simultaneous and separated administration in hFcRn-transgenic mice. IVIg did not affect the PK profile of efgartigimod (gMG, SC Submission).

Effect of Efgartigimod on the PK and PD of Concomitant Medications

Efgartigimod may potentially affect the PK and/or PD of compounds that bind to the human FcRn (ie, immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass). Because of its mechanism of action, efgartigimod affects the elimination of therapeutic IgGs, including IVIg.

As described in the gMG IV submission, no clinically relevant effect on PK and PD of therapeutic antibodies and immunoglobulins is expected when an antibody is given 2 weeks or later after the last efgartigimod PH20 SC injection.

2.3.4. Pharmacodynamics

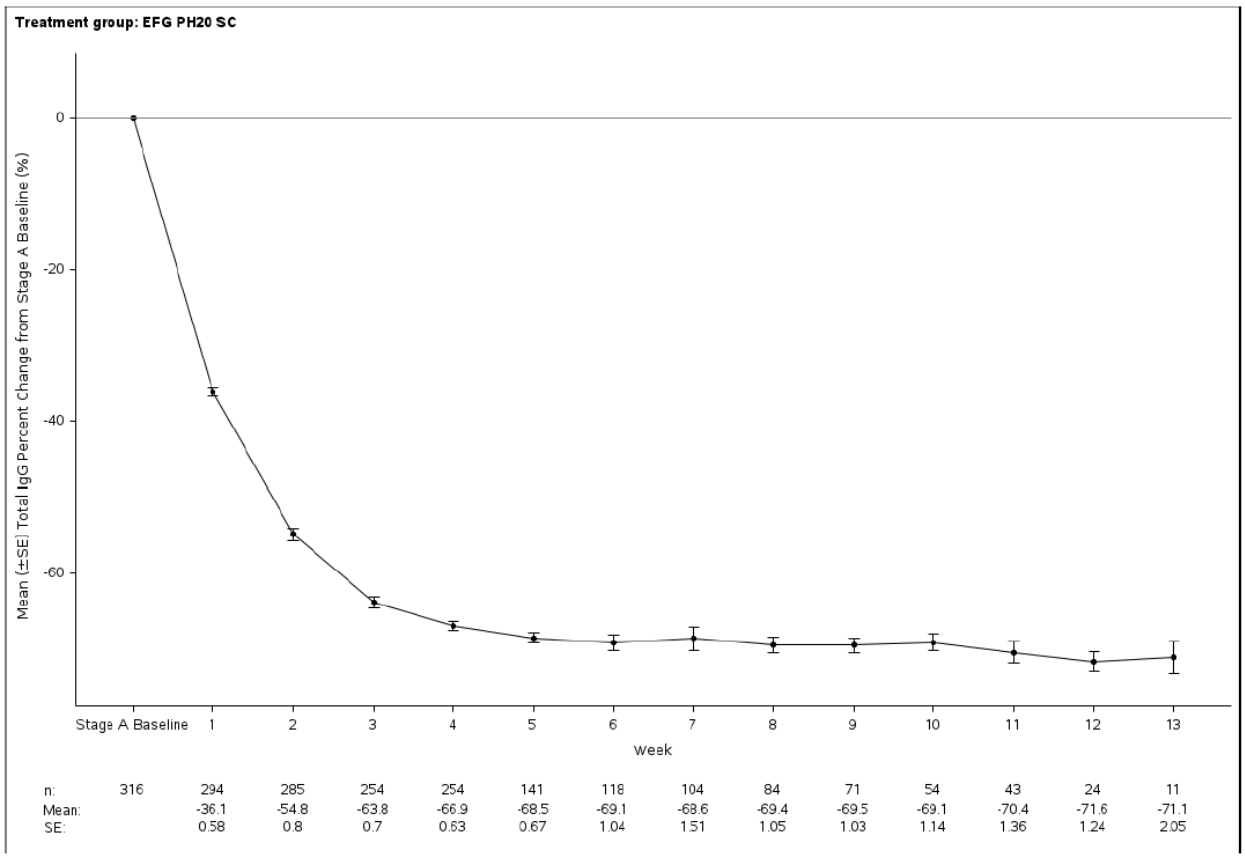
Mechanism of action

The FcRn has a specific role in IgG homeostasis and recycles all IgG subtypes (IgG1, IgG2, IgG3, IgG4), rescuing them from intracellular lysosomal degradation. FcRn binds to pinocytosed IgG and protects the IgG from transport to degradative lysosomes by recycling it back to the extracellular compartment. This FcRn-mediated recycling accounts for the longer half-life and higher plasma concentrations of IgGs compared to other immunoglobulins that are not recycled by FcRn. Efgartigimod alfa is a human IgG1 Fc-fragment modified to have an increased affinity to FcRn. Efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated recycling of IgGs and results in increased IgG degradation including pathogenic IgG autoantibodies. Compared to the wild-type Fc fragment, efgartigimod has significantly increased affinity for human FcRn at both neutral and acidic pH.

Primary and secondary pharmacology

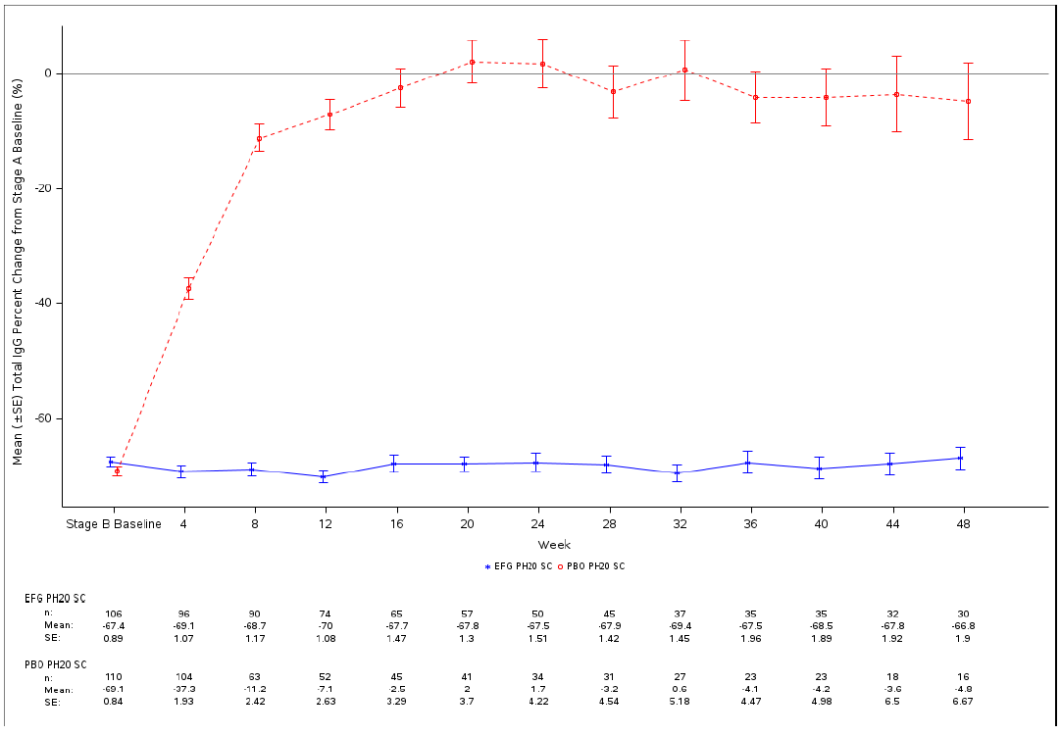
Consistent with its mechanism of action, efgartigimod PH20 SC reduced total IgG levels. Once-weekly efgartigimod PH20 SC administration resulted in rapid total IgG reductions during the first 4 weeks of treatment. With continued weekly dosing, the mean (SE) percentage change in total IgG levels was sustained throughout the treatment period, ranging from −66.8 (1.90)% to −71.6 (1.24)% between week 4 until the end of Stage B of ARGX-113-1802 (efgartigimod PH20 SC arm). In participants randomized to placebo in Stage B of ARGX-113-1802, total IgG levels had returned to baseline (approximately 10% reduction from baseline) by week 8 (Figure 23 and Figure 24).

Figure 23: Study ARGX-113-1802, Stage A: Mean Percent Change From Stage A Baseline Over Time in Total IgG in Participants With CIDP (Overall Population)



CIDP=chronic inflammatory demyelinating polyneuropathy; CSR=clinical study report; efgartigimod/EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IgG=immunoglobulin γ; IMP=investigational medicinal product; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: This study applies a once-weekly dosing schedule. If efgartigimod PH20 SC treatment is ceased, total IgG levels start to increase again. Therefore, samples taken more than 2 weeks after the last IMP administration are excluded from the analysis (*post hoc*). The analysis with all samples included is similar but with more variability and presented in the CSR

Figure 24: Study ARGX-113-1802, Stage B: Mean Percent Change From Stage A Baseline Over Time in Total IgG in Participants With CIDP (Overall Population)



SC=efgartigimod for SC administration coformulated with rHuPH20; IgG=immunoglobulin γ; IMP=investigational medicinal product; n=number of participants for whom the observation was reported; PBO PH20 SC=placebo coformulated with rHuPH20 for SC administration; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: This study applies a once-weekly dosing schedule. If efgartigimod PH20 SC treatment is ceased, total IgG levels start to increase again. Therefore, samples taken more than 2 weeks after the last IMP administration are excluded from the analysis (post hoc). The analysis with all samples included is similar but with more variability and presented in the CSR

2.3.5. Discussion on clinical pharmacology

Bioanalytical methods

The bioanalytical program (PK, PD and ADA assays) was fulfilling and well documented.

PK/PD models

A popPK model was developed for CIDP patients based on a previous 3-compartment model developed for HV and subjects with gMG, using a pre-DBL data set from Study ARGX-113-1802. Study ARGX-113-1802 was a 2-stage study in patients with CIDP: first a 12-week treatment stage A (Q1W 1000 mg efgartigimod PH20 SC) followed by a split 1:1 placebo or treatment stage B for treatment responders in Stage A. Sampling was sparse and pre-dose only. The parameters were estimated with good precision but the eta shrinkage was large except on CL. During cross-validation, the ECLIA assay at REDACTED resulted in lower PK concentrations than the sandwich immunoassay, and a bioassay factor of 0.82 was included on IPRED in the PK model under the assumption the effect was similar across the dynamic range.

A PK/total IgG model described the Total IgG concentration data from Study ARGX-113-1802. Of note, data from participants with Stage A only were not included in the VPCs of reduction of Total IgG, only those subjects who responded to treatment and were allowed to continue to Stage B. Observed Stage A total IgG baseline was added as a covariate effect for the total IgG baseline parameter to adjust for effects of prior CIDP medication. Of note, only few study participants were real treatment naïve prior to study enrolment. The VPC for reduction of Total IgG for pre-treated subjects (Figure 16), indicated that pretreated subjects with Stage A only (non-responders) had a similar reduction in Total IgG than the

ones who were treatment-responders and allowed to continue to Stage B implying that reduction in IgG is not directly linked to treatment efficacy.

Pharmacokinetics of efgartigimod in CIDP patients

Efgartigimod was dosed once weekly with no drug holidays to CIDP patients. Exposure to efgartigimod in study 1802 and 1902 was followed at one single time point, namely C_{trough} as samples were collected only at predose. Exposure at C_{though} remained stable through the study at 15-20 µg/mL in patients receiving efgartigimod. Japanese patients were sampled around C_{max} (48 and 96 hours) after the first and fourth dose showing mean serum concentrations of 23 and 43 µg/mL, respectively. The PopPK model showed no meaningful differences in PK with regard to race or ethnicity. In participants who entered the Stage B placebo arm, the efgartigimod serum concentrations decreased to levels below the limit of quantification (0.200 µg/mL) after 5 weeks.

Section 5.2 of the SmPC was updated with the following paragraph: "*In patients receiving continuous subcutaneous administration of efgartigimod alfa 1000 mg once weekly, mean C_{trough} ranged from 14.9 to 20.1 mcg/mL*". This is considered valuable information as it shows that the continuous posology of efgartigimod SC for the CIDP indication elicits similar C_{trough} values as the IV and SC posology for the gMG indication within the treatment cycles.

Efgartigimod showed dose proportionality (750–1750 mg) and lack of time dependency as presented in the previous submission (gMG SC). This was confirmed in CIDP patients.

The flat dose of 1000 mg is the same as for the gMG SC indication. However, the posology for the CIDP indication is different from the gMG indication, as for CIDP continuous weekly administrations are recommended (as used in the CIDP clinical study), whereas in the gMG indication, cycles of 4 weekly injections with subsequent treatment cycle no sooner than 7 weeks from the start of the previous treatment is recommended (as used in the gMG clinical study). Even though the posology in CIDP is more aggressive than in gMG patients, who are systematically given drug holidays (cyclic treatment), the Applicant demonstrated with patient data, that even if efgartigimod is accumulating in rare cases, this precipitated no safety implications. Moreover, the posology for CIDP can be changed to every other week according to clinical evaluation. Since efgartigimod appear well-tolerated using the posology of continuous once weekly administration, the justification of dose and posology for CIDP is considered acceptable.

Intersubject variability of C_{trough} serum concentrations of efgartigimod was moderate and increased slightly from Stage A (19.3-55.8%) to Stage B in study 1802 (49.3-59.6%).

Using PKPD modelling, body weight, age, sex at birth, race and ethnicity was not found to impact pharmacokinetics (CL, V or exposure).

As for the gMG indication, mild renal impairment was found to slightly increase exposure to efgartigimod due to decreased clearance. The wording in section 5.2 of the SmPC is amended with specific results from the covariate analysis of CIDP patients with mild renal impairment (11% to 21% increase in exposure) in lieu of the word "limited".

No patients with hepatic impairment were included in the studies. Markers of hepatic function as covariates in the POPPK model were not found to impact pharmacokinetics of efgartigimod.

Pharmacodynamics

Participants with CIDP treated with efgartigimod have a sustained reduction of IgG compared to pre-treatment levels, which supports the proposed pharmacodynamic effects of efgartigimod. Going into Stage A differences in IgG levels, depending on the type of previous treatment with immunosuppressants, were observed. However, the level of and %change from baseline IgG was similar

across prior treatment (CS, immunoglobulins and no treatment directly before run-in). This suggests that no significant carry-over effect is present from a pharmacodynamic point-of-view.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology data are considered acceptable for the extension of indication. The product information has been updated accordingly.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were conducted for CIDP. For the dose justification please refer to section Clinical Pharmacology.

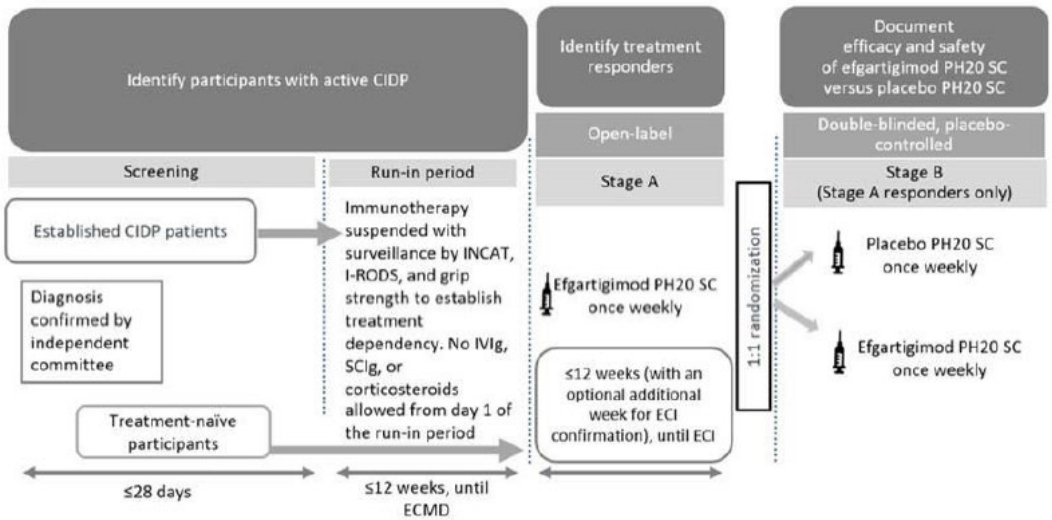
2.4.2. Main study

ARGX-113-1802

The clinical efficacy of efgartigimod PH20 SC in participants with CIDP is supported by 2 clinical studies. The pivotal phase 2 study ARGX-113-1802 and the ongoing, open-label study ARGX-113-1902, which is an extension of ARGX-113-1802. ARGX-113-1902 is considered a supportive study and described at the end of this section.

The pivotal phase 2 study ARGX-113-1802 (Figure 25) was a prospective, multisite study on the efficacy, safety, tolerability, immunogenicity, PK and PD of efgartigimod PH20 SC in adult participants diagnosed with probable or definitive CIDP (as established by an independent committee of experts). The study was conducted as a randomized withdrawal study in 2 treatment stages: an open-label Stage A in which responders to efgartigimod PH20 SC were identified, and a randomized-withdrawal, double-blinded, placebo-controlled Stage B. The primary analysis of ARGX-113-1802 was planned when 88 events (relapses) occurred in Stage B, upon which the study was stopped.

Figure 25: ARGX-113-1802 Study design



Methods

Study participants

The key inclusion criteria for this study were:

- Aged ≥18 years, diagnosed with probable or definite CIDP, using European Academy of Neurology/Peripheral Nerve Society (EFNS/PNS criteria), progressing or relapsing forms
- CDAS score ≥2 at screening
- Inflammatory neuropathy cause and treatment (INCAT) score ≥2 at the first visit of the run-in period or Stage A baseline (treatment-naïve patients with documented evidence for worsening). Participants with an INCAT score of 2 had to have this score exclusively from the leg disability score; for participants with an INCAT score of ≥3, there were no specific requirements for arm or leg scores. The run-in period was applicable for non–treatment-naïve participants or treatment-naïve participants with no documented evidence of worsening on the aINCAT disability score within 3 months before screening. Treatment-naïve participants with documented evidence for worsening on the aINCAT disability score within 3 months before screening, compared to the previous aINCAT score within 6 months before screening, could enter Stage A directly. Participants in the run-in period started Stage A if they had ECMD (evidence of clinically meaningful deterioration) during the run-in period.
- Fulfilled any of the following treatment conditions:
    - Treated (ie, within the last 6 months) with pulsed corticosteroids, oral corticosteroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg, and willing to discontinue this treatment at the first run-in visit; OR
    - Treatment-naïve, defined as:
        - without previous CIDP treatment; OR
        - not treated with monthly or daily corticosteroids, IVIg, or SCIg for at least 6 months before screening

The key exclusion criteria for this study were:

- Pure sensory atypical CIDP
- Polyneuropathy of other causes (including IgM monoclonal gammopathy with anti-MAG antibodies)
- Any other disease that could better explain the participant's signs and symptoms
- Any history of myelopathy or evidence of central demyelination
- 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, tumour 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.

Screening and run-in period

To reduce the risk of enrolling participants who had been misdiagnosed, the participant's CIDP diagnosis, as determined by the investigator, was reviewed by an independent adjudication committee during the screening period of ARGX-113-1802. This committee comprised neurologists with at least 10 years of experience in diagnosing CIDP. Participants whose diagnosis could not be verified were not eligible.

Before entering Stage A, participants must show evidence of clinical deterioration, to allow selection of patients with active disease. Participants receiving corticosteroids, IVIg, or SCIg at screening entered a run-in period during which all CIDP treatment was discontinued. If participants had ECMD (evidence of clinically meaningful deterioration) during the run-in period they were included in Stage A.

ECMD included:

- ≥1 point increase from baseline in aINCAT, and/or
- ≥4 points decrease from baseline in Inflammatory Rasch-built Overall Disability Scale (I-RODS), and/or
- ≥8 kPa decrease from baseline in mean grip strength

Treatment-naïve participants with recent evidence of clinical deterioration (documented worsening on the aINCAT score within 3 months prior to screening) entered Stage A directly from the screening period. Treatment-naïve participants without recent evidence of clinical deterioration entered the run-in period until they had ECMD.

Monitoring during run-in

Patients are monitored by grip strength, I-RODS score, Medical Research Council (MRC) sum score, aINCAT score, and the Timed Up and Go (TUG) test. 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 electronic case report form (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.

Stage A

All participants entering the open-label Stage A had active disease and initiated once-weekly injections of efgartigimod PH20 SC for up to 12 weeks with a minimum of 4 administrations. Stage A lasted until ECI was confirmed, and participants without confirmed ECI within 12 weeks were classified as non-responders.

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: o 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. o 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. o 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.

Monitoring during Stage A

Each patient will remain in Stage A and return weekly to the trial site (including physical exam, aINCAT, MRC, I-RODS, TUG and grip strength) until ECI relative to Stage A baseline has been identified by the evaluating investigator at 2 consecutive visits. 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 and attend a follow-up visit 28 days after the last administration of efgartigimod.

Stage B

Participants with ECI, confirmed at 2 consecutive visits in Stage A, were randomized at Stage B baseline in a 1:1 ratio to receive once-weekly efgartigimod PH20 SC or placebo. Participants can only be entered in Stage B if they show improvement in aINCAT score during Stage A (decrease ≥1 point versus Stage A baseline). If no change in aINCAT is observed during Stage A, non-treatment naïve patients can enter Stage B, ***if*** ECMD, upon entry to stage A, was based on deterioration on I-RODS/grip strength during the run-in period, and improvement in these were observed during Stage B. Stage B lasted up to 48 weeks. Participants who had clinical deterioration (ie, event; confirmed worsening in aINCAT score by 1 point or unconfirmed worsening on aINCAT score ≥ 2 points) or completed week 48 in Stage B, without clinical deterioration, were withdrawn from the study and could continue efgartigimod PH20 SC treatment in the OLE study.

Follow-up was done 28 days after the final dose of efgartigimod (if the participant did not roll over to the OLE study ARGX-113-1902). The total study duration for each participant was up to 80 weeks, with a maximum cumulative treatment period of 61 weeks.

Monitoring during Stage B

All patients randomized to the double-blind, randomized-withdrawal Stage B will be dosed with efgartigimod weekly but will return to the clinic once every 4 weeks. At each of these visits, specific procedures will be performed including aINCAT score, MRC sum score, I-RODS score, mean grip strength, TUG test and for some visits patient reported outcome such as EuroQol 5 Dimensions and 5 Levels Health-related Quality-of-Life Questionnaire (EQ-5D-5L).

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 (e.g, confirmation of worsening on the adjusted INCAT score of 1 point), or 4) any other reason. If the unscheduled visit is used to confirm clinical deterioration during run-in or Stage B, the assessments as listed for the scheduled visits in the corresponding period will need to be performed.

Overall versus pre-treated population

Results for ARGX-113-1802 are presented for two populations; the overall population and the pre-treated population. The clinical development of efgartigimod PH20 SC for CIDP was performed in participants who were naïve to CIDP treatment (corticosteroids or immunoglobulins) within the 6 months before screening and those who received either corticosteroids or immunoglobulins within the 6 months before screening. These participants comprise the "overall population," and their data form the basis of this submission.

A prespecified subgroup was identified that included participants who had received CIDP therapy within the 6 months before screening and had a CDAS score of ≥4 at screening. This subgroup, called the "pretreated population," represents 43.2% of the overall population in Stage A and supports the indication statement for the EU label.

Treatments

Wash-out of ongoing CIDP treatments was done in the run-in period. Participants may have received pulsed corticosteroids, oral steroids equivalent to prednisolone/prednisone ≤10 mg/day, and/or IVIg or SCIg within 6 months before screening and had to stop their treatment at the first run-in visit to allow for the evaluation of efgartigimod PH20 SC in the absence of potentially confounding concomitant medications. No other CIDP treatments were allowed after wash-out.

Investigational medicinal product (IMP) will be administered to all patients in Stage A as efgartigimod PH20 SC 1000 mg 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 (patients who show ECI only at the last visit in Stage A will be allowed to extend Stage A for a further week with one additional consecutive visit and a 13th injection of IMP to evaluate confirmed ECI). IMP in Stage B will be either efgartigimod PH20 SC 1000 mg or placebo PH20 SC, administered in the abdominal skin area. During Stage B, all patients will receive IMP weekly up to 48 weeks.

Objectives

Primary objectives of ARGX-113-1802

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. ECI observed at 2 consecutive study visits between weeks 4 and 12 classified the participant as a responder.

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.

Secondary objectives of ARGX-113-1802

Secondary objectives of Stage A and Stage B are the following:

- To assess the time to clinical improvement (Stage A only).
- 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.

Outcomes/endpoints

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. The (principal) investigator at the centre cannot take the role of the evaluating 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 cannot be involved in evaluating aINCAT, I-RODS, mean grip strength, MRC or TUG test. However, the treating physician will have access to results of ECI and ECMD assessments.

The **evaluating physician** will oversee the scoring of:

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

The evaluating physician will make the assessment of clinical deterioration. Throughout the whole duration of the trial, the evaluating physician will not seek nor collect any treatment-related information (e.g, 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 Adverse Events (AE)s, 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.

Efficacy instruments

CIDP CDAS score

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(14)):

1 Cure: ≥ 5 years off treatment A Normal examination or B Abnormal examination, stable/improving

2. Remission < 5 years off treatment A Normal examination or B Abnormal examination, stable/improving

3. Stable active disease ≥1 year, on treatment A Normal examination or B Abnormal examination, stable/improving

4. Improvement ≥ 3 months < 1 year, on treatment A Normal examination or B Abnormal examination, stable/improving

5. Unstable active disease abnormal examination with progressive or relapsing course* A treatment naïve or < 3 months, or B off treatment or C On treatment.

The classification is based upon the clinal assessment of the treatment physician tat the time of the last evaluation.

* 5B and 5C refer to patients who were treatment refractory from prior therapy or worsening despite ongoing therapy.

INCAT and adjusted INCAT (aINCAT)

The INCAT score 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 (aINCAT), 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. As such, the aINCAT is a more conservative score than the total INCAT score.

Three different baseline INCAT scores are recorded during the trial. 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
- Baseline Stage A = Total INCAT score at the first visit of Stage A
- Baseline Stage B = Total INCAT score at the first visit of Stage B

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.

MRC Score

The 6-point MRC sum score evaluates motor strength/weakness.

- 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 (arm abductors, elbow flexors, wrist extensors) and lower limbs (hip flexors, knee extensors, foot dorsiflexors) in order to obtain a summed score between 0 and 60.

I-RODS

The I-RODS is a patient reported outcome measure on disability and assesses the limitations of activities and social participation in patients with inflammatory neuropathies. 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). Although the I-RODS, as a PRO, can be considered subjective, the scale has been shown to correlate well with grip strength, which is a direct measure of muscle strength. When assessed at home, the patient will record the measurements.

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.

TUG Test

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

EQ-5D-5L

Quality of life will be assessed through the EQ-5D-5L. It is a standardized instrument for use as a measure of health.

Brief Pain Inventory – Short Form (BPI-SF)

The Brief Pain Inventory Short Form (BPI-SF) is a validated, self-administered questionnaire designed to measure a patient’s perceived level of pain and the impact of this pain on the patient’s daily functioning. The BPI-SF measures the patient’s intensity of pain (sensory dimension), the interference of pain in the patient’s life (reactive dimension), and asks the patient about pain relief, pain quality, and the patient’s perception of the cause of pain. The BPI-SF consists of 9 items that use a numeric rating scale to assess pain severity and pain interference in the past 24 hours.

Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM questionnaire was developed to measure patients’ satisfaction with their medication using 3 scales (effectiveness, convenience, and global satisfaction). The TSQM-9 was found to be a reliable and valid measure to assess treatment satisfaction in naturalistic trial designs, in which there is potential that the administration of the side effects domain of the original TSQM would interfere with routine clinical care.

Rasch-transformed-Fatigue Severity Scale (RT-FSS)

The original Fatigue Severity Scale (FSS) was a 9-item scale to measure the severity of fatigue and its impact on the patient’s daily activities and life style. It was found that a 7-item RT-FSS gave a more proper assessment of fatigue in patients with immune-mediated neuropathies. Therefore, in this trial, the abbreviated RT-FSS will be used.

Hospital Anxiety and Depression Scale (HADS)

HADS aims to measure symptoms of anxiety and depression in people with physical health problems. HADS is a 14-item scale with 7 items related to anxiety and 7 to depression. HADS is widely used and has been validated.

Patient Global Impression of Change (PGIC)

The self-report measure PGIC reflects a patient's belief about the efficacy of treatment. PGIC is a 7-point scale depicting a patient's rating of overall improvement.

Endpoints

Primary endpoints

Stage A: percentage of participants with confirmed ECI during Stage A.

Stage B: time to first clinical deterioration compared to Stage B baseline (defined as an increase in ≥1 point in aINCAT score 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

Stage A

- Time to initial confirmed ECI during Stage A
- Change from Stage A baseline over time in: aINCAT score; MRC sum score; 24-item I-RODS score; TUG score; Mean grip strength assessed by Martin-Vigorimeter
- Change from Stage A baseline over time during Stage A in EQ-5D-5L
- Changes in serum IgG levels (total IgG) over time during Stage A

Stage B

- Time to CIDP disease progression (defined as the time from the first dose of double-blinded IMP to the first I-RODS score decrease ≥4 points compared with Stage B baseline using the centile metric).
- Percentage of participants with improved functional level compared to Stage B baseline as measured by an increase in the 24-item I-RODS score (increase ≥4 points vs baseline) up to week 48
- Change from Stage B baseline over time in: aINCAT score; MRC sum score; 24-item I-RODS score; TUG score; Mean grip strength assessed by Martin-Vigorimeter
- Time to 10% decrease in the 24-item I-RODS score during Stage B
- Change from Stage B baseline over time during Stage B in EQ-5D-5L
- Changes in serum IgG levels (total IgG) over time during Stage B

Exploratory endpoints of ARGX-113-1802

Change from Stage A baseline over time during Stage A and change from Stage B baseline over time during Stage B, in the following patient-reported outcomes (PROs): Brief Pain Inventory Short Form (BPI-SF); TSQM-9; RT-FSS; HADS; PGIC.

Sample size

Under the assumption that the hazard ratio of efgartigimod PH20 SC to placebo is 0.50, 88 events were required in Stage B to provide 90% power to demonstrate that the time to first occurrence of clinical deterioration is different in the efgartigimod PH20 SC arm compared with the placebo arm at a 2-sided alpha level of 0.05 using a log-rank test. Participants were randomized into Stage B until 88 events occurred per the sample size calculation. The study ended when the 88th event occurred.

Randomisation

Stage A: Not applicable as stage A was single armed.

Stage B: participants were randomized to efgartigimod PH20 SC or placebo in a 1:1 ratio. Participants were stratified according to their prior CIDP medication and the decrease of adjusted INCAT score during Stage A.

- Prior CIDP medication: Treatment-naïve; 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.

Blinding (masking)

Stage A is single armed.

Stage B: 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. The trial will be unblinded following the final database lock.

Statistical methods

Efficacy analyses sets:

Stage A: Safety analysis set (SAF-A): Participants from the screened participants set who received at least one dose or part of a dose of IMP in Stage A.

Stage B: Modified intent-to-treat (mITT): Participant who were randomized in Stage B and who received at least one dose or part of a dose of IMP in Stage B. Per protocol (PP): Participants from the mITT analysis set without major protocol deviations.

Analysis methods for primary endpoint, Stage A.

The summary measure of Stage A is the percentage of participants with confirmed ECI during Stage A (ECI-responders). The percentage of ECI responders on efgartigimod PH20 SC will be calculated along with 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.

The definition of ECI is given above in the section on monitoring. It is based on aINCAT, I-RODS and grip strength score. Confirmed ECI is defined as fulfilling the criteria for improvement (ECI) at 2 consecutive visits on the same efficacy parameter (with no missed CRF visit(s) in between). Additionally,

the participant must have received at least 4 doses. Confirmed ECI will be derived based on the scheduled and unscheduled visits as collected per CRF.

Sub-groups and sensitivity analyses in Stage A, primary endpoint:

The following subgroups are defined for the Stage A efficacy analysis:

- Confirmed ECI response: ECI responders (response ≤ 4 weeks) / ECI responders (4 weeks < response ≤ 8 weeks) / ECI responders (8 weeks <response < before EOSA) / ECI responders (total) / ECI non-responders.
- Stage A Treatment duration: ≤ 4 weeks / 4 weeks - ≤ 8 weeks) / > 8weeks
- Prior CIDP medication at screening: treatment-naïve / corticosteroids / IVIg or SCIg (see section 3.3.2).
- ECMD worsening on adjusted INCAT: yes/no.
- ECMD worsening on I-RODS (only for I-RODS table): yes/no.
- ECMD worsening on MGS (only for MGS table): yes/no.

Treatment-naïve participants for whom no ECMD is determined will be classified as 'no'.

As a sensitivity analysis on the primary Stage A endpoint, a frequency tabulation will also be provided for the number and percentage of confirmed ECI responders (and exact two-sided Clopper-Pearson 95% CI), only including participants that were not ongoing in stage A at the time the 88th event in Stage B occurred. This table will be repeated by prior CIDP medication at screening.

As a second sensitivity analysis on the primary Stage A endpoint, a frequency tabulation will be provided for the number and percentage of confirmed ECI responders as assessed by the investigator (with exact two-sided Clopper-Pearson 95% CI).

It is noted that prior CIDP medicine is investigated.

Table 10 includes the historical controls the applicant wishes to compare to the obtained results. There is no formal statistical hypothesis.

Table 10: Historical control data

Study	Treatment	Rate (%)	Lower limit 95% C.I	Upper limit 95% C.I
ICE (Hughes et al, 2008)	Active	47.5	34.298365	60.8807104
	Placebo	22.4	12.508919	35.2723899
PATH (van Schaik et al, 2018)	Active	72.9	66.352194	78.8714163
PRIMA (Léger et al, 2013)	Active	60.7	40.576821	78.4957171
ProCID (Cornblath et al, 2022)	Active	79.7	68.306983	88.4396379

Analysis methods for primary endpoint, Stage B.

Primary and alternative estimands

The primary objective of Stage B is to determine the efficacy of efgartigimod PH20 SC compared to placebo based on the time to occurrence of the first evidence of clinical deterioration. Use of prohibited medicine is allowed and treatment discontinuation regardless of reason is considered non-informative and censored. To accomplish this objective the following primary estimand is constructed in accordance with the ICH E9 (R1) addendum:

- Population: mITT population

- Treatment condition: efgartigimod PH20 SC versus placebo
- Endpoint: time to first adjusted INCAT deterioration compared to Stage B baseline (clinical deterioration). Clinical deterioration will only consider adjusted INCAT score
- Population summary measure: hazard ratio for efgartigimod PH20 SC versus placebo model with Wald-type 95% CI
- Main intercurrent events (ICEs) and the strategies to handle them are presented in Table 11.

Table 11: Stage B Primary estimand – main intercurrent events and strategies

ICE	Strategy for primary estimand
Early withdrawal from trial for efficacy related reason (patient lost to follow-up, consent withdrawn, physician's decision, prohibited medication, lack of treatment efficacy).	While-on-treatment: data up to the ICE will be used in the analysis. Patients who do not experience adjusted INCAT deterioration before the ICE are censored at the time of last observed INCAT assessment.
Early withdrawal from trial due to COVID-19 infection.	While-on-treatment: see above.
Early withdrawal from trial for other reason, including patients who have to discontinue the trial early when the trial is stopped (when all events for the primary analysis are achieved).	While-on-treatment: see above.
Temporary treatment interruption (see section 3.6.2) or early treatment discontinuation (but patient continues trial).	Treatment policy: data will be used in the analysis regardless of whether a patient experienced the ICE or not.
Use of prohibited medications (see section 3.4.2) (but patient continues trial).	Treatment policy: see above.
Death.	While-on-treatment (while-alive): see above.
COVID-19 infection (but patient continues trial).	Treatment policy: see above.

The primary hypothesis for stage B evaluates this estimand:

- Null hypothesis: The hazard ratio of efgartigimod PH20 SC compared to placebo is 1
- Alternative hypothesis: The hazard ratio of efgartigimod PH20 SC compared to placebo is ≠1

Participants who complete the study or withdraw for any reason before experiencing adjusted INCAT deterioration will be censored at the time of last observed INCAT assessment. Participants who withdraw without any post-baseline INCAT assessments will be censored at time of first dose. Censoring is considered non-informative. In summary, withdrawal (missing data) for whatever reason is censored. If data are non-missing it is used regardless of intercurrent event.

Alternative treatment of intercurrent events to test the robustness of the primary estimand:

Extreme Case Analysis:

Following ICEs will be considered as an event in addition to the primary analysis:

- Death or withdrawal from the study for any reason (except participants withdrawn from study because of the occurrence of the 88th event in Stage B).
- Participants who have to discontinue the study early when the study is stopped (when all 88 events for the primary analysis are achieved) and who have an increase of the adjusted INCAT score of 1 point at their final INCAT assessment without a followed confirmation will also be considered as having an event of clinical deterioration.

Mixed-case analysis:

Following ICEs will be considered as an event in addition to the primary analysis:

- Death or withdrawal from study for efficacy related reason (participant lost to follow-up, consent withdrawn, physician's decision, prohibited medication, lack of treatment efficacy).
- Participants who have to discontinue the study early when the study is stopped (when all 88 events for the primary analysis are achieved) and who have an increase of the adjusted INCAT score of 1 point at their final INCAT assessment without a followed confirmation will also be considered as having an event of clinical deterioration.

Method for estimation of hazard ratio and test:

Time to first adjusted INCAT deterioration compared to Stage B baseline will be analyzed using a Cox proportional hazard model (main estimator for the primary estimand) with a fixed categorical effect for treatment (with placebo as reference). The model will be stratified by prior CIPD medication and decrease of adjusted INCAT score during Stage A. The hazard ratio for efgartigimod PH20 SC versus placebo model will be provided along with the corresponding Wald-type 95% CI and 2-sided p-value at the 0.05 significance level. The p-value is testing the primary hypothesis that the hazard ratio is one.

The proportional hazard assumption will be assessed within each stratum using a log-log plot of the survival function and by plotting the Schoenfeld residuals over time.

Method for Constructing and Comparing Survival Curves (Time to Worsening) for Treatment vs. Placebo

A Kaplan-Meier time to event analysis for time to adjusted INCAT deterioration will also be provided. The number and percentage of events and censored observations (overall and by censoring reason), median and percentiles with 95% CI and the log rank test (stratified for prior CIPD medication and decrease of adjusted INCAT score during Stage A) will be provided. In addition, the estimated percentage of participants with adjusted INCAT deterioration at Week 24 and Week 48, with 95% confidence interval will be provided.

Sensitivity analyses:

The Cox proportional hazard model and Kaplan-Meier analysis for time to adjusted INCAT deterioration will be repeated (sensitivity analyses):

- Analysis will be repeated on the PP population;
- Analysis will be repeated on the mITT population, but excluding participants who did not have confirmed ECI in Stage A;
- Analysis will be repeated using the sensitivity endpoints for time to deterioration (extreme-case analysis, mixed-case analysis, based On investigator's assessment);
- Analysis will be repeated using actual stratification values.
- Analysis will be repeated by stratification factors:

- Prior CIPD medication at screening: treatment-naïve / corticosteroids / IVIg or SCIg;
- Decrease of adjusted INCAT score in Stage A: no change / decrease of ≥ 1 point;

Note: the stratification by which the analysis is repeated will not be included in the Cox proportional hazard model.

- Analysis will be repeated by subgroups

Of Note, the analysis using actual stratification values anticipates that some patients will be randomized based on an incorrect stratification factor. 6 patients were mis-stratified. The "Note" presented above by the applicant clarifies that when the actual strata are included in the analysis, the strata according to randomisation will not be included in the model.

Subgroup analyses:

The following subgroups are defined for the Stage B efficacy analysis:

- Sex at birth: Male / Female.
- Region: North-America / Asia / Europe / ROW (rest of world).
- Race: White / Black or African American / Asian / Other.
- Age group: 18 - < 65 years / ≥ 65 years.
- Body weight: <50, 50-<75, 75-<100, 00-<125, ≥ 125
- Body mass index (BMI) at screening: Underweight: < 18.5 kg/m2; Normal weight: 18.5 -<25 kg/m2; Overweight: 25 -< 30 kg/m2; Obese: >= 30 kg/m2
- CDAS score at screening: 1 / 2 – 4 / 5.
- Stage B Treatment duration: ≤ 8 weeks / 8 weeks - ≤ 26 weeks / > 26 weeks (descriptive statistics over time only)

Subgroups with less than 10 participants in total will not be shown for subgroup analyses.

Analysis methods for secondary efficacy endpoints for Stage A and Stage B.

Stage A:

The time to initial confirmed ECI will be analysed using Kaplan-Meier time to event analysis.

Adjusted INCAT disability score, MRC total scores, I-RODS centile metric score, TUG test score and mean grip strength (dominant hand and non-dominant hand) will be summarized by means of descriptive statistics at each analysis visit and at the last assessment.

Stage B

Time to CIDP disease progression will be analysed by the same methodology as the primary endpoint.

Improved functional level will be analysed using an exact logistic regression model with fixed categorical effect for treatment and stratified by stratification factors.

The time to 10% decrease in I-RODS will be analysed using Kaplan-Meier time to event analysis.

Adjusted INCAT disability score, MRC total scores, I-RODS centile metric score, TUG test score and mean grip strength (dominant hand and non-dominant hand) will be summarized by means of descriptive statistics at each analysis visit.

Sensitivity and sub-group analyses are exhaustive and of note, interaction with prior CIDP medication is investigated where relevant.

Results

ARGX-113-1802 is the pivotal study and results are presented for two sub-populations:

Overall population: all enrolled participants; analyses in the overall population form the basis of this submission and demonstrate the efficacy of efgartigimod PH20 SC in participants with CIDP.

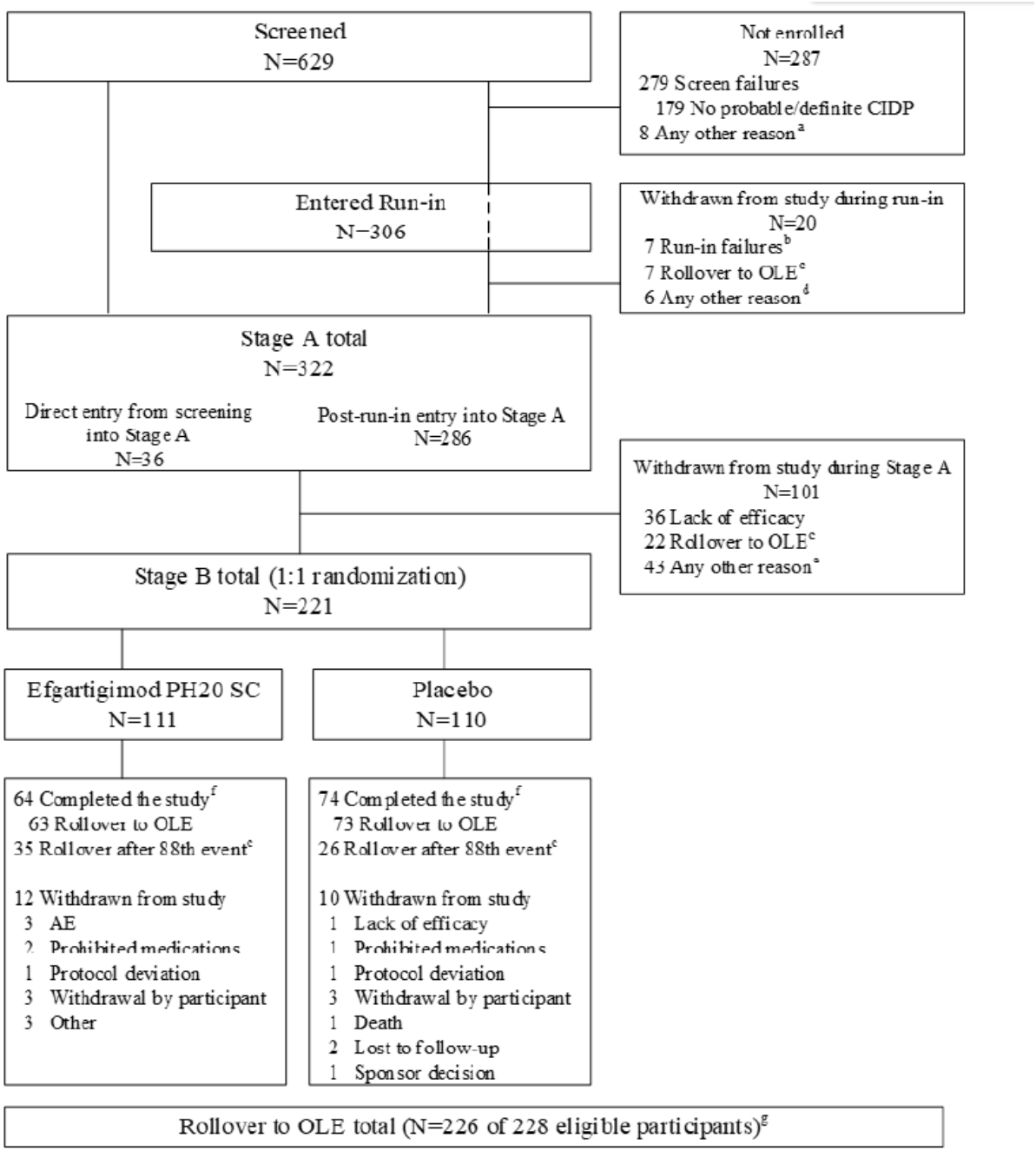
Pretreated population: a subgroup comprising participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening; prespecified analyses in the pretreated population support the proposed indication in the EU for the treatment of adult patients with CIDP with active disease despite treatment with corticosteroids or immunoglobulins.

Participant flow

Overall population

In Stage A, 322 participants received open-label efgartigimod PH20 SC; the mean (SD) duration of treatment was 5.2 (3.28) weeks. The median (min, max) number of efgartigimod PH20 SC administrations was 4 (1, 13). In Stage B, 111 participants in the SAF-B received efgartigimod PH20 SC and 110 participants received placebo; the mean (SD) duration of treatment was 25.1 (17.17) and 18.7 (16.88) weeks, respectively. The median (min, max) number of IMP administrations per participant was 22.0 (2.0, 48.0) and 12.0 (2.0, 48.0) in the efgartigimod PH20 SC and placebo arms, respectively. Participant disposition is displayed in Figure 26.

Figure 26: Study ARGX-113-1802 Participant disposition – Overall population



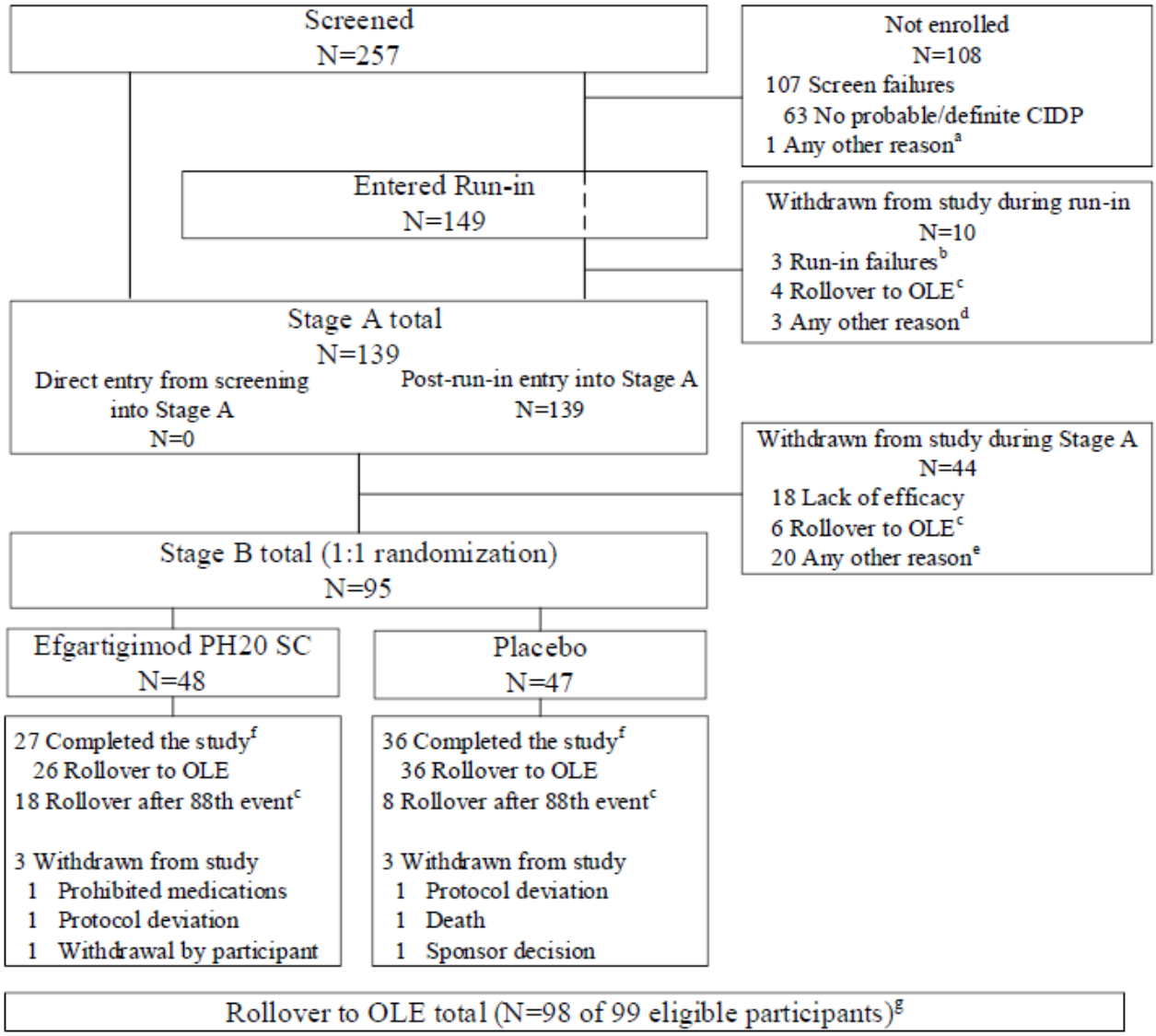
AE=adverse event; ECMD=evidence of clinically meaningful deterioration; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; OLE=open-label extension; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
a Any other reason includes: 1 physician decision, 1 sponsor decision, 5 withdrawal by participant, and 1 other.
b Run-in failures include participants who did not have ECMD during the run-in period.
c These participants rolled over into the OLE after the 88th event in Stage B.
d Any other reason includes 2 physician decision, 1 prohibited medication, 1 sponsor decision, and 2 withdrawal by participant.
e Any other reason includes 20 AEs, 1 death, 2 lost to follow-up, 1 IMP noncompliance, 1 physician decision, 2 prohibited medications, 11 withdrawal by participant, and 5 other.
f Completed the study indicates that a participant had an event or completed the study.
g In total, 226 of 228 eligible participants rolled over to the OLE (7/7 participants ongoing in the run-in period at the 88th event; 22/22 participants ongoing in Stage A; 35/35 participants ongoing in the efgartigimod PH20 SC arm of Stage B; 26/26 participants ongoing in the placebo arm in Stage B; 63/64 participants in the efgartigimod PH20 SC arm who completed Stage B; and 73/74 participants in the placebo arm who completed Stage B).

Pretreated population

A total of 139 pretreated participants were enrolled and treated in Stage A, which represents 43.2%

(139/322) of the overall population. In Stage B, 95 (68.3%) participants from Stage A in the pretreated population were randomized in a 1:1 ratio to receive either efgartigimod PH20 SC or placebo (48 and 47 in the efgartigimod PH20 SC and placebo arms, respectively). Participant disposition is displayed in Figure 27.

Figure 27: Study ARGX-113-1802 Participant disposition – Pretreated population.



AE=adverse event; CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; ECMD=evidence of clinically meaningful deterioration; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; OLE=open-label extension; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Note: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening.

a The reason for not enrolling was a withdrawal by participant.

b Run-in failures include participants who did not have ECMD during the run-in period.

c These participants rolled over into the OLE after the 88th event in Stage B.

d The 3 "Any other reason" are 2 "physician decision" and 1 withdrawal by the participant.

e Any other reason includes 6 AEs, 1 death, 1 lost to follow-up, 1 physician decision, 1 prohibited medication, 6 withdrawal by participant, and 4 other.

f Completed the study indicates that a participant had an event or completed the study.

g In total, 98 of 99 eligible participants rolled over to the OLE (4/4 participants ongoing in the run-in period at the 88th event; 6/6 participants ongoing in Stage A; 18/18 participants ongoing in the efgartigimod PH20 SC arm of Stage B; 8/8 participants ongoing in the placebo arm in Stage B; 26/27 participants in the efgartigimod PH20 SC arm who completed Stage B; and 36/36 participants in the placebo arm who completed Stage B).

Recruitment

A total of 146 sites in Austria, Belgium, Bulgaria, China, Denmark, France, Georgia, Germany, Israel, Italy, Japan, the Netherlands, Poland, Romania, Russian Federation, Serbia, Spain, Taiwan, Turkey, Ukraine, the United Kingdom, and the United States enrolled participants in Stage A. Participants in Stage B were enrolled from these same countries, except for Turkey, which enrolled 0 participants in Stage B.

Table 12: Participants enrolled in Stage A based on geographical location (overall population)

Region, n (%)	
North America	48 (14.9)
Asia	87 (27.0)
Europe (EU/EEA/EFTA/UK)	130 (40.4)
Rest of the world	57 (17.7)

Table 13: Participants enrolled in Stage B based on geographical location (overall population)

	Efgartigimod PH20 SC (N=111)	**Placebo (N=110)**	**Total (N=221)**
Region, n (%)			
North America	14 (12.6)	17 (15.5)	31 (14.0)
Asia	32 (28.8)	34 (30.9)	66 (29.9)
Europe (EU/EEA/EFTA/UK)	40 (36.0)	37 (33.6)	77 (34.8)
Rest of the world	25 (22.5)	22 (20.0)	47 (21.3)

Study initiation date (first participant first visit): 15 Apr 2020

Study completion date (last participant last visit): 11 May 2023

Final CSR report date: 21 Nov 2023

Conduct of the study

The original protocol, version 1.0 (30 Oct 2019), was amended 4 times: 2.0 (10 Jan 2020), 3.0 (04 May 2020), 4.0 (30 Nov 2020), and 5.0 (12 Oct 2022). Substantial changes in the conduct of the study are described in Table 14.

Table 14: Substantial changes in global protocol amendments

Global Amendments

Version 2.0, 10 Jan 2020 (no participants were enrolled in protocol version 1.0)	The primary endpoint of Stage B was updated: 1. The time window for confirmation of the first occurrence of clinical deterioration (defined by an increase of ≥1 point in aINCAT score compared with Stage B baseline) was shortened to reduce the time of clinical deterioration and offer follow-up treatment as soon as possible. 2. A clarification was added that to prevent further deterioration, no confirmation was needed for a clinical deterioration (increase in aINCAT score of ≥2 points compared with baseline). Clarification of the eligibility criterion was added: The lowest possible INCAT score of 2 had to be exclusively from leg disability.
Version 3.0, 04 May 2020	COVID-19 mitigation measures were added. Additional IMP blinding measures were added (using blinded IMP vials and masked syringes). A withdrawal criterion was added for Stage A. The requirement of a 4-week minimum in the run-in period before entering Stage A was removed.
Version 4.0, 30 Nov 2020	The definition of ECI was updated to include I-RODS and/or grip strength (for participants with no change in aINCAT during run-in). Inclusion criterion #6 was updated to specify that "current" CIDP treatment at screening means "within the last 6 months." Based on nonclinical teratogenicity and reproductive toxicity data, female participants could use acceptable contraception methods (in addition to highly effective methods) and male contraception was no longer required; however, male participants had to agree not to donate sperm during the study and for 90 days after. Clarification was added for INCAT scores at baseline (with different baselines during the study) and aINCAT scores at postbaseline visits. The safety section was updated based on the current Investigator's Brochure at the time of the amendment.
	Further clarification was provided on how to perform a home visit during the COVID-19 pandemic.

Version 5.0, 12 Oct 2022	EQ-5D-5L was escalated from an exploratory endpoint to a secondary endpoint. As an additional blinding precaution, local IgG measurements were no longer allowed, and total protein and albumin results were not sent to the sites (or not measured if a local laboratory was used) after the Stage B baseline. IgG subtype measurements were removed from the protocol. A change was made to allow participants in the run-in period at the time the study stopped (ie, at the 88th event) to roll over to the OLE study. The maximum number of 180 randomized participants in Stage B was removed. Clarification was added that additional tests could be performed to confirm the CIDP diagnosis. The list of prohibited medications was updated. Based on nonclinical teratogenicity and reproductive toxicity data, the inclusion and exclusion criteria were updated: 1) Female participants could stop their contraception method at the date of the last IMP dose; 2) Female participants could become pregnant immediately after the study; 3) Male participants could donate sperm. Integration of country-specific requirements (except for China) in the global protocol.

Protocol deviations

In **SAF-A (Stage A safety analysis set, n = 322)** 46 (14.3%) participants had major protocol deviations. The most common major deviation during the run-in period and Stage A was treatment deviation (28 [8.7%] participants). Major treatment deviations that occurred more than once included:

- ECI not observed during Stage A, per protocol, but the participant was randomized to Stage B
- Participant had a temporary interruption of IMP for >10% of the total planned doses.

Two participants had protocol deviations determined violations of study eligibility criteria. None of the major protocol deviations impacted the interpretation of the Stage A study data.

In the **SAF-B (Stage B safety analysis set, n = 221)** 37 (16.7%) participants had major protocol deviations: 15 (13.5%) participants in the efgartigimod PH20 SC arm and 22 (20.0%) participants in the placebo arm. Overall, the most common major protocol deviation was treatment deviation (25 [11.3%] participants). Major treatment deviations that occurred more than once included:

- participant received IMP that was not stored/handled in correct conditions
- participant had a temporary interruption of IMP for >10% of the total planned doses
- participant received treatment that was different from the assigned treatment

None of the major protocol deviations impacted the interpretation of the Stage B data (Table 15).

Table 15: Protocol deviation for participants in the SAF-B (minor deviation not shown).

	Efgartigimod PH20 SC (N=111)	Placebo (N=110)	Total (N=221)
No deviations	4 (3.6)	3 (2.7)	7 (3.2)
Any major deviation	15 (13.5)	22 (20.0)	37 (16.7)
Excluded concomitant medication	4 (3.6)	2 (1.8)	6 (2.7)
Selection criteria not met	1 (0.9)	3 (2.7)	4 (1.8)
Treatment deviation	9 (8.1)	16 (14.5)	25 (11.3)
Participant not withdrawn from the study per protocol	0	1 (0.9)	1 (0.5)
Other	2 (1.8)	1 (0.9)	3 (1.4)

efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per arm in the SAF-B; n=number of participants with data; rHuPH20=recombinant human hyaluronidase PH20; SAF-B=Stage B safety analysis set; SC=subcutaneous(ly)

Ethical considerations

Independent Ethics Committee and/or Institutional Review Board: The protocol, protocol amendments, final approved ICFs, relevant supporting information, and participant recruitment information were approved by the IEC/IRB and regulatory agency before participants were enrolled.

Ethical Conduct of the Study: This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, applicable ICH GCP guidelines, and applicable laws and regulations.

Participant Information and Consent: Evaluation of eligibility was performed at screening and confirmed at visit 1. The participant's informed consent was documented by the dated signature of the participant (and assent, if applicable) and the dated signature of the investigator or investigator's delegate.

Baseline data

Overall population

Stage A

ARGX-113-1802 enrolled a global (North America, Asia, Europe, and rest of world) CIDP population. The median (min, max) age of participants in Stage A was 56.0 (20.0, 82.0) years. The majority of the Stage A participants were male (64.6%) and White (65.5%); 89 (27.6%) participants were Asian. The median (min, max) time since CIDP diagnosis in Stage A was 2.8 (0, 46) years. Approximately half (51.2%) of the participants in Stage A had received IVIg or SCIg as the most recent prior CIDP therapy before enrolment, 63 (19.6%) had received corticosteroids as the most recent prior CIDP therapy before enrolment, and 94 (29.2%) had not received CIDP treatment for at least 6 months before screening. Baseline disease characteristics of overall population at A-Stage are shown in Table 16.

Table 16: Baseline Disease Characteristics (SAF-A) Efgartigimod (overall population)

	Efgartigimod PH20 SC (N=322)
Entry status Stage A, n (%)	
Entered Stage A from screening	36 (11.2)
Non–treatment-naïve	0
Treatment-naïve	36 (11.2)
Evidence of worsening	35 (10.9)
No evidence of worsening	1 (0.3)
Entered Stage A from run-in with	286 (88.8)
No ECMD	4 (1.2)
ECMD	282 (87.6)
Time since CIDP diagnosis (years)	
n	322
Mean (SD)	4.9 (6.09)
Median (min, max)	2.8 (0, 46)
CIDP diagnosis[a], n (%)	
Typical CIDP	268 (83.2)
Atypical CIDP	54 (16.8)
Asymmetric	29 (9.0)
Distal	20 (6.2)
Pure motor	5 (1.6)
CIDP disease evolution, n (%)	
Relapsing	147 (45.7)
Progressive	174 (54.0)
Unknown	1 (0.3)
CIDP disease activity status, n (%)	
2 to 4	125 (38.8)
5	197 (61.2)
Prior CIDP therapy (screening), n (%)	
Corticosteroids	63 (19.6)
IVIg or SCIg	165 (51.2)
Treatment-naïve	94 (29.2)

Total INCAT score at Stage A baseline	
n	317
Mean (SD)	4.6 (1.67)
Median (min, max)	4.0 (2, 9)
I-RODS score at Stage A baseline	
n	321
Mean (SD)	40.1 (14.67)
Median (min, max)	40.0 (0, 100)
Mean grip strength – dominant hand – Stage A baseline (kPa)	
n	318
Mean (SD)	38.5 (24.18)
Median (min, max)	38.5 (0, 107)
Mean grip strength – nondominant hand – Stage A baseline (kPa)	
n	318
Mean (SD)	39.0 (24.71)
Median (min, max)	38.5 (0, 119)

INCAT=inflammatory neuropathy cause and treatment; CCC=CIDP confirmation committee; CIDP=chronic inflammatory demyelinating polyneuropathy; ECMD=evidence of clinically meaningful deterioration; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ICF=informed consent form; IVIg=intravenous immunoglobulin; I-RODS=Inflammatory Rasch-built Overall Disability Scale; max=maximum; min=minimum; N=number of participants in SAF-A; n (for categorical data)=number of participants for whom the observation was reported; n (for continuous data)=number of participants with data; rHuPH20=recombinant human hyaluronidase PH20; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SCIg=subcutaneous immunoglobulin
Notes: Time since CIDP diagnosis (years) was calculated as follows: (date of ICF – date of diagnosis)/365.25. Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥6 months before screening. The denominator for the percentage calculations was the total number of participants in SAF-A, excluding missing values.
a The CIDP diagnosis was determined by the investigator and verified by the CCC.

Stage B

The median (min, max) age was 56.0 (22, 82) years in the efgartigimod PH20 SC arm and 54.5 (20, 78) years in the placebo arm. The median (min, max) time since CIDP diagnosis was 2.1 (0, 22) years and 2.2 (0, 29) years in the efgartigimod PH20 SC and placebo arms, respectively, in Stage B. The percentage of participants who had received prior IVIg or SCIg CIDP therapy was 44.1% in the efgartigimod PH20 SC arm and 42.7% in the placebo arm in Stage B. Participants who previously received corticosteroids comprised 23.4% of participants in the efgartigimod PH20 SC arm and 21.8% in the placebo arm in Stage B compared to 19.6% in Stage A. Treatment-naïve participants comprised 32.4% of participants in the efgartigimod PH20 SC arm and 35.5% in the placebo arm in Stage B. The mean (SD) treatment duration was longer in the efgartigimod PH20 SC arm than in the placebo arm (25.1 [17.17] and 18.7 [16.88] weeks, respectively). The median (min, max) number of IMP administrations per participant was 22.0 (2.0, 48.0) and 12.0 (2.0, 48.0) in the efgartigimod PH20 SC and placebo arms, respectively. Baseline disease characteristics of overall population at B-Stage are shown in Table 17.

Table 17: Baseline Disease Characteristics (SAF-B) Efgartigimod (overall population)

	Efgartigimod PH20 SC (N=111)	**Placebo (N=110)**	**Total (N=221)**
Entry status of Stage B, n (%)			
No evidence of ECI	4 (3.6)	9 (8.2)	13 (5.9)
Evidence of ECI	107 (96.4)	101 (91.8)	208 (94.1)
Time since CIDP diagnosis (years)			
n	111	110	221
Mean (SD)	3.7 (4.40)	3.8 (4.68)	3.8 (4.53)
Median (min, max)	2.1 (0, 22)	2.2 (0, 29)	2.2 (0, 29)
CIDP diagnosis[a], n (%)			
Typical CIDP	97 (87.4)	95 (86.4)	192 (86.9)
Atypical CIDP	14 (12.6)	15 (13.6)	29 (13.1)
Asymmetric	6 (5.4)	7 (6.4)	13 (5.9)
Distal	7 (6.3)	7 (6.4)	14 (6.3)
Pure motor	1 (0.9)	1 (0.9)	2 (0.9)
CIDP disease evolution, n (%)			
Relapsing	49 (44.1)	53 (48.2)	102 (46.2)
Progressive	62 (55.9)	57 (51.8)	119 (53.8)
CIDP disease activity status, n (%)			
2-4	37 (33.3)	34 (30.9)	71 (32.1)
5	74 (66.7)	76 (69.1)	150 (67.9)
Prior CIDP therapy, n (%)			
Corticosteroids	26 (23.4)	24 (21.8)	50 (22.6)
IVIg or SCIg	49 (44.1)	47 (42.7)	96 (43.4)
Treatment-naïve	36 (32.4)	39 (35.5)	75 (33.9)
Stratification factor – prior CIDP therapy, n (%)			
IVIg or SCIg	48 (43.2)	48 (43.6)	96 (43.4)
Corticosteroids	24 (21.6)	23 (20.9)	47 (21.3)
Treatment-naïve	39 (35.1)	39 (35.5)	78 (35.3)
Stratification factor – aINCAT score during Stage A, n (%)			
aINCAT score decrease of ≥1 point during Stage A	75 (67.6)	75 (68.2)	150 (67.9)
No decrease in aINCAT score during Stage A	36 (32.4)	35 (31.8)	71 (32.1)

Total INCAT score at Stage B baseline			
n	111	110	221
Mean (SD)	3.1 (1.51)	3.3 (1.57)	3.2 (1.54)
Median (min, max)	3.0 (0, 8)	3.0 (0, 7)	3.0 (0, 8)
I-RODS score at Stage B baseline			
n	111	110	221
Mean (SD)	53.6 (17.91)	51.2 (15.37)	52.4 (16.70)
Median (min, max)	51.0 (19, 100)	48.0 (22, 100)	50.0 (19, 100)
Mean grip strength – dominant hand – Stage B baseline (kPa)			
n	111	110	221
Mean (SD)	54.9 (23.64)	58.0 (25.09)	56.5 (24.36)
Median (min, max)	56.0 (0, 105)	54.5 (0, 125)	55.0 (0, 125)
Mean grip strength – nondominant hand – Stage B baseline (kPa)			
n	111	110	221
Mean (SD)	55.4 (28.29)	56.7 (24.80)	56.0 (26.56)
Median (min, max)	55.0 (0, 203)	52.5 (3, 117)	53.0 (0, 203)

(a)INCAT=(adjusted) inflammatory neuropathy cause and treatment; CCC=CIDP confirmation committee; CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ICF=informed consent form; I-RODS=inflammatory-Rasch-built Overall Disability Scale; IVIg=intravenous immunoglobulin; max=maximum; min=minimum; N=number of participants per treatment arm in SAF-B; n (for categorical data)=number of participants for whom the observation was reported; n (for continuous data)=number of participants with data; SCIg=subcutaneous immunoglobulin; rHuPH20=recombinant human hyaluronidase PH20; SAF-B=Stage B safety analysis set; SC=subcutaneous(ly)
a The CIDP diagnosis was determined by the investigator and verified by the CCC.
Notes: Time since CIDP diagnosis (years) was calculated as follows: (date of ICF – date of diagnosis)/365.25. Stratification factors show the categories as randomized. Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥6 months before screening. The denominator for the percentage calculations was the total number of participants per treatment arm in SAF-B, excluding missing values.

Results for the mITT population were identical to those for the SAF-B population.

Pretreated population

Stage A

In Stage A, the median (min, max) age of participants in the pretreated population was 55.0 (21.0, 80.0) years. The majority of the Stage A participants were male (63.3%) and White (57.6%); 46 (33.1%) participants were Asian. The median (min, max) time since CIDP diagnosis in Stage A was 2.1 (0, 25) years. Before enrolment, the most recent prior CIDP therapy was IVIg or SCIg in 102 (73.4%) participants and corticosteroids in 37 (26.6%) participants. Baseline disease characteristics of pretreated population at A-Stage are shown in Table 18.

Table 18: Baseline Disease Characteristics (SAF-A) Efgartigimod (pretreated population)

	Efgartigimod PH20 SC (N=139)
Entry status Stage A, n (%)	
Entered Stage A from screening	0
Entered Stage A from run-in with	139 (100.0)
No ECMD	1 (0.7)
ECMD	138 (99.3)
Time since CIDP diagnosis (years)	
n	139
Mean (SD)	4.4 (5.53)
Median (min, max)	2.1 (0, 25)
CIDP diagnosis[a], n (%)	
Typical CIDP	113 (81.3)
Atypical CIDP	26 (18.7)
Asymmetric	14 (10.1)
Distal	9 (6.5)
Pure motor	3 (2.2)
CIDP disease evolution, n (%)	
Relapsing	67 (48.2)
Progressive	72 (51.8)
CIDP disease activity status, n (%)	
4	21 (15.1)
5	118 (84.9)
Prior CIDP therapy (screening), n (%)	
Corticosteroids	37 (26.6)
IVIg or SCIg	102 (73.4)
Total INCAT score at Stage A baseline	
n	139
Mean (SD)	4.9 (1.86)
Median (min, max)	4.0 (2, 9)
I-RODS score at Stage A baseline	
n	139
Mean (SD)	37.5 (15.96)
Median (min, max)	37.0 (0, 100)

Mean grip strength – dominant hand – Stage A baseline (kPa)	
n	138
Mean (SD)	34.4 (25.50)
Median (min, max)	33.0 (0, 105)
Mean grip strength – nondominant hand – Stage A baseline (kPa)	
n	138
Mean (SD)	34.4 (24.87)
Median (min, max)	33.0 (0, 103)

CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; INCAT=inflammatory neuropathy cause and treatment; CCC=CIDP confirmation committee; CIDP=chronic inflammatory demyelinating polyneuropathy; ECMD=evidence of clinically meaningful deterioration; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ICF=informed consent form; IVIg=intravenous immunoglobulin; I-RODS=Inflammatory Rasch-built Overall Disability Scale; max=maximum; min=minimum; N=number of participants in SAF-A; n (for categorical data)=number of participants for whom the observation was reported; n (for continuous data)=number of participants with data; rHuPH20=recombinant human hyaluronidase PH20; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SCIg=subcutaneous immunoglobulin
Notes: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The time since CIDP diagnosis (years) was calculated as follows: (date of ICF − date of diagnosis)/365.25. The denominator for the percentage calculations was the total number of participants in SAF-A, excluding missing values. a The CIDP diagnosis was determined by the investigator and verified by the CCC.

Stage B

The median (min, max) age was 55.5 (26, 73) years in the efgartigimod PH20 SC arm and 48.0 (21, 78) years in the placebo arm. The median (min, max) time since CIDP diagnosis was 1.1 (0, 22) years and 2.0 (0, 15) years in the efgartigimod PH20 SC and placebo arms, respectively, in Stage B. The percentage of participants who had received prior IVIg or SCIg CIDP therapy was 68.8% in the efgartigimod PH20 SC arm and 63.8% in the placebo arm in Stage. Participants who previously received corticosteroids comprised 31.3% of participants in the efgartigimod PH20 SC arm and 36.2% in the placebo arm in Stage B. Baseline disease characteristics of pretreated population at B-Stage are shown in Table 19.

Table 19: Baseline Disease Characteristics (SAF-B) Efgartigimod (pretreated population)

	Efgartigimod PH20 SC (N=48)	**Placebo (N=47)**	**Total (N=95)**
Entry status of Stage B, n (%)			
No evidence of ECI	2 (4.2)	4 (8.5)	6 (6.3)
Evidence of ECI	46 (95.8)	43 (91.5)	89 (93.7)
Time since CIDP diagnosis (years)			
n	48	47	95
Mean (SD)	3.1 (4.32)	3.6 (4.02)	3.4 (4.16)
Median (min, max)	1.1 (0, 22)	2.0 (0, 15)	1.5 (0, 22)

CIDP diagnosis[a], n (%)			
Typical CIDP	44 (91.7)	40 (85.1)	84 (88.4)
Atypical CIDP	4 (8.3)	7 (14.9)	11 (11.6)
Asymmetric	1 (2.1)	3 (6.4)	4 (4.2)
Distal	3 (6.3)	3 (6.4)	6 (6.3)
Pure motor	0	1 (2.1)	1 (1.1)
CIDP disease evolution, n (%)			
Relapsing	25 (52.1)	26 (55.3)	51 (53.7)
Progressive	23 (47.9)	21 (44.7)	44 (46.3)
CIDP disease activity status, n (%)			
4	8 (16.7)	4 (8.5)	12 (12.6)
5	40 (83.3)	43 (91.5)	83 (87.4)
Prior CIDP therapy (actual), n (%)			
Corticosteroids	15 (31.3)	17 (36.2)	32 (33.7)
IVIg or SCIg	33 (68.8)	30 (63.8)	63 (66.3)
Stratification factor – prior CIDP therapy, n (%)			
IVIg or SCIg	32 (66.7)	30 (63.8)	62 (65.3)
Corticosteroids	14 (29.2)	15 (31.9)	29 (30.5)
Treatment-naïve[b]	2 (4.2)	2 (4.3)	4 (4.2)
Stratification factor − aINCAT score during Stage A, n (%)			
aINCAT score decrease of ≥1 point during Stage A	32 (66.7)	33 (70.2)	65 (68.4)
No decrease in aINCAT score during Stage A	16 (33.3)	14 (29.8)	30 (31.6)
Total INCAT score at Stage B baseline			
n	48	47	95
Mean (SD)	3.3 (1.67)	3.0 (1.62)	3.1 (1.64)
Median (min, max)	3.0 (0, 8)	3.0 (0, 7)	3.0 (0, 8)
I-RODS score at Stage B baseline			
n	48	47	95
Mean (SD)	52.3 (18.55)	53.6 (16.18)	53.0 (17.34)
Median (min, max)	51.0 (19, 100)	50.0 (22, 100)	51.0 (19, 100)
Mean grip strength – dominant hand – Stage B baseline (kPa)			
n	48	47	95
Mean (SD)	50.2 (25.25)	59.4 (27.41)	54.8 (26.61)
Median (min, max)	50.0 (0, 105)	53.0 (0, 125)	51.0 (0, 125)

Mean grip strength – nondominant hand – Stage B baseline (kPa)			
n	48	47	95
Mean (SD)	51.1 (25.23)	57.0 (27.78)	54.1 (26.54)
Median (min, max)	50.0 (5, 105)	53.0 (3, 115)	52.0 (3, 115)

(a)INCAT=(adjusted) inflammatory neuropathy cause and treatment; CCC=CIDP confirmation committee;

CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ICF=informed consent form; I-RODS=Inflammatory-Rasch-built Overall Disability Scale; IVIg=intravenous immunoglobulin; max=maximum; min=minimum; N=number of participants per treatment arm in SAF-B; n (for categorical data)=number of participants for whom the observation was reported; n (for continuous data)=number of participants with data; SCIg=subcutaneous immunoglobulin; rHuPH20=recombinant human hyaluronidase PH20; SAF-B=Stage B safety analysis set; SC=subcutaneous(ly)

Notes: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The time since CIDP diagnosis (years) was calculated as follows: (date of ICF – date of diagnosis)/365.25. Stratification factors show the categories as randomized. Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥6 months before screening. The denominator for the percentage calculations was the total number of participants per treatment arm in SAF-B, excluding missing values.

a The CIDP diagnosis was determined by the investigator and verified by the CCC.

b For these 4 participants, the actual stratification factor differed from the stratification factor in the randomization list. All 4 participants received prior CIDP treatment. Minor protocol deviations were reported for all4 participants for incorrect stratification factors (Section 10.2).

Results for the mITT analysis set were identical to those for the SAF-B.

Numbers analysed

The numbers analysed per each population or analysis set are displayed in the Table 20, Table 21, Table 22 and Table 23.

Overall population

Table 20: Number of participants in each population or analysis set (Stage A)

	Efgartigimod PH20 SC **n**
SAF-A	322
PK analysis set	321
PD analysis set	321
Immunogenicity analysis set	322

Efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; n=number of participants per analysis set; PD=pharmacodynamics; PK=pharmacokinetics; rHuPH20=recombinant human hyaluronidase PH20; SAF-A= Stage A safety analysis set; SC=subcutaneous(ly)

Table 21: Number of participants in each population or analysis set (Stage B)

	Efgartigimod PH20 SC n	Placebo n	Total n
All randomized participants ITT	111	110	221
SAF-B	111	110	221
PK analysis set	111	110	221
PD analysis set	111	110	221
Immunogenicity analysis set	111	110	221
mITT analysis set	111	110	221
PP analysis set	96	88	184

Efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ITT=intent-to-treat; mITT=modified intent-to-treat; n=number of participants per analysis set; PD=pharmacodynamics; PK=pharmacokinetics; PP=per protocol; rHuPH20=recombinant human hyaluronidase PH20; SAF-B= Stage B safety analysis set; SC=subcutaneous(ly).
The mITT analysis set was identical to the SAF-B population

Pretreated population

Table 22: Number of participants in the pretreated population Stage A by Population and analysis set

	Efgartigimod PH20 SC n
SAF-A	139
PK analysis set	139
PD analysis set	139
Immunogenicity analysis set	139

CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; n=number of participants per analysis set; PD=pharmacodynamics; PK=pharmacokinetics; rHuPH20=recombinant human hyaluronidase PH20; SAFA= Stage A safety analysis set; SC=subcutaneous(ly)
Note: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening.

Table 23: Number of participants in the pretreated population Stage B by Population and analysis set

	Efgartigimod PH20 SC	Placebo	Total
All randomized participants ITT	48	47	95
SAF-B	48	47	95
PK analysis set	48	47	95
PD analysis set	48	47	95
Immunogenicity analysis set	48	47	95
mITT analysis set	48	47	95
PP analysis set	39	39	78

CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ITT=intent-to-treat; mITT=modified intent-to-treat; PD=pharmacodynamics; PK=pharmacokinetics; PP=per protocol; rHuPH20=recombinant human hyaluronidase PH20; SAF-B=Stage B safety analysis set; SC=subcutaneous(ly)
Note: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening.
Results for the mITT analysis set were identical to those for the SAF-B

Outcomes and estimation

A) STAGE A

Overall population: Primary endpoint

During Stage A, 214 (66.5%) participants had confirmed ECI (primary endpoint; 95% CI, 61.0-71.6).

Table 24: Confirmed ECI Responders (SAF-A) (Stage A – Primary Endpoint)

	Efgartigimod PH20 SC (N=322)	
	n (%)	Exact 2-sided Clopper-Pearson 95% CI
Number of participants with confirmed ECI	214 (66.5)	61.0-71.6
Number of participants without confirmed ECI	108 (33.5)	
Completed Stage A treatment without confirmed ECI	21 (6.5)	
Discontinued treatment in Stage A	87 (27.0)	
Ongoing in Stage A at 88th event in Stage B	18 (5.6)	
Discontinued early for other reasons	69 (21.4)	

ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants in SAF-ArHuPH20=recombinant human hyaluronidase PH20; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly)
Notes: All participants in SAF-A who did not have confirmed ECI were considered ECI nonresponders, including participants ongoing in Stage A at the occurrence of the 88th event in Stage B. The denominator for the percentage calculations was the total number of participants in SAF-A.

The primary analysis included ongoing participants (at time of the 88th event in Stage B) without ECI as nonresponders; therefore, a prespecified sensitivity analysis for the ECI responder analysis was performed, which excluded all participants who were ongoing in Stage A at the time of the last participant's last visit. Based on this sensitivity analysis, a higher percentage (95% CI) of participants (214 [70.4% (64.9-75.5)] participants) had confirmed ECI when ongoing Stage A participants were excluded.

ECI responders by prior treatment (within ≤ 6 months before screening)

Confirmed ECIs were observed in 49 (77.8%) participants receiving prior corticosteroids, 97 (58.8%) participants receiving prior IVIg or SCIg, and 68 (72.3%) treatment-naïve participants. A higher percentage (66 [40.0%]) of participants in the IVIg or SCIg subgroup than in the corticosteroids (12 [19.0%]) and treatment-naïve (15 [16.0%]) subgroups discontinued Stage A treatment early (after they had stopped IVIg or SCIg in the run-in period and had been required to demonstrate evidence of clinically meaningful deterioration).

Because week 4 was the earliest time point at which the ECI criteria could have been met, participants who discontinued treatment before week 4 (ie, before 4 treatment administrations plus 1 additional week for ECI confirmation) would not have been in the study long enough to have ECI (and to have a maximum reduction in total IgG). To evaluate response rates in participants who were in the study long enough to meet ECI criteria, a *post hoc* analysis was performed excluding those with <4 treatment administrations. Excluding participants with <4 treatment administrations, the number of participants in the IVIg or SCIg subgroup decreased from 165 to 123 (25.5%), compared with a decrease of 63 to 61 (3.2%) and 94 to 91 (3.2%) in the corticosteroid and treatment-naïve subgroups, respectively. Of participants with ≥4 administrations, the percentage with confirmed ECI was comparable across prior CIDP therapy subgroups (49 participants [80.3%] receiving prior corticosteroids, 97 [78.9%] receiving prior IVIg or

SCIg, and 68 [74.7%] who were treatment-naïve), indicating that the higher number of early treatment discontinuations before the onset of a treatment effect at week 4 in the IVIg or SCIg subgroup contributed to the lower response rate in this subgroup.

Table 25: Confirmed ECI Responders by prior CIDP Therapy at screening (SAF-A) (Stage A – Primary Endpoint-Subgroup analysis)

	Efgartigimod PH20 SC (N=322)		
	Corticosteroids (N=63) n (%)	IVIg or SCIg (N=165) n (%)	Treatment-naïve (N=94) n (%)
Number of participants with confirmed ECI (95% CI)	49 (77.8) (65.5-87.3)	97 (58.8) (50.9-66.4)	68 (72.3) (62.2-81.1)
Number of participants without confirmed ECI	14 (22.2)	68 (41.2)	26 (27.7)
Completed Stage A treatment without confirmed ECI	2 (3.2)	8 (4.8)	11 (11.7)
Discontinued treatment in Stage A	12 (19.0)	60 (36.4)	15 (16.0)
Ongoing in Stage A at 88th event in Stage B	4 (6.3)	7 (4.2)	7 (7.4)
Discontinued early for other reasons	8 (12.7)	53 (32.1)	8 (8.5)

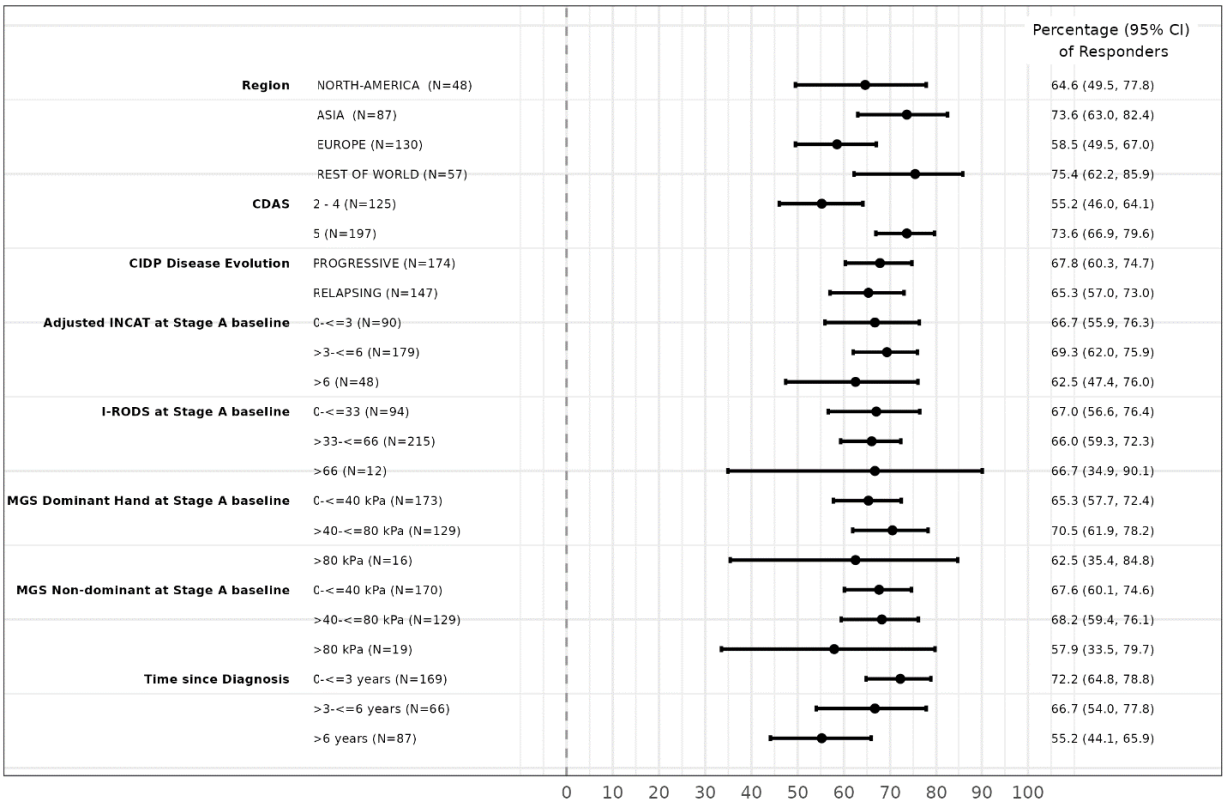
CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20;IVIg=intravenous immunoglobulin; N=number of participants per treatment group/prior CIDP therapy subgroup in SAF-A; rHuPH20=recombinant human hyaluronidase PH20; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SCIg=subcutaneous immunoglobulin.
Notes: treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ⩾6 months before screening. All participants in SAF-A who did not have confirmed ECI were considered ECI nonresponders, including participants ongoing in Stage A at the occurrence of the 88th event in Stage B. The denominator for the percentage calculations was the total number of participants in SAF-A

ECI responders by way of deterioration in run-in

ECI responders were stratified by way of deterioration during the run-in phase. In the treatment-naïve group n = 35 entered Stage A based on previous evidence of worsening (aINCAT score), 25/35 had ECI (71.4%). In the population coming from the run-in phase (n = 286), a total of n=114 (39.8%) had demonstrated ECMD on aINCAT score, of these n=74 had ECI (64.9%). The remaining patients in Stage A had no change in aINCAT during run (n=168), but demonstrated ECMD by I-RODS/grip strength deterioration. Of these, 68.5% had ECI.

***Post Hoc* subgroup analysis of confirmed ECI responders**

Figure 28: Forest Plot of confirmed ECI responders by subgroup (SAF-A) (Stage A-Primary endpoint-Post hoc subgroup analysis)



CDAS=CIDP Disease Activity Status; CI=confidence interval; CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; INCAT=inflammatory neuropathy cause and treatment; I-RODS=Inflammatory Rasch-built Overall Disability Scale; MGS=mean grip strength; N=number of participants per subgroup in the SAF-A; SAF-A=Stage A safety analysis set

A higher percentage of ECI responders was observed in participants with a CDAS of 5 (73.6%) than those with a CDAS of 2 to 4 (55.2%). The percentage of participants with an ECI response was also higher in participants with more recently diagnosed disease (0 to ≤3 years; 72.2%) compared with those with a time since diagnosis of >6 years (55.2%). A lower percentage of responders was observed in Europe (58.5%) and North America (64.6%) compared with Asia (73.6%) and ROW (75.4%). Europe and North America had a higher percentage of participants who received prior IVIg or SCIg therapy (73.8% and 62.5%, respectively) compared with Asia and ROW (37.9% and 10.5%, respectively).

Pretreated population: <u>Primary endpoint</u>

During Stage A, 94 (67.6%) participants in the pretreated population had confirmed ECI (primary endpoint; 95% CI, 59.2-75.3). In total, n=36 (25.9%) discontinued treatment in Stage A. Based on a sensitivity analysis excluding ongoing participants in Stage A, at the 88th event in Stage B, a higher percentage (95% CI) of participants (94 [69.1% (60.6-76.8)] participants) had confirmed ECI. This is similar to the overall population.

ECI responders by prior treatment (within ≤ 6 months before screening)

The number and percentage of confirmed ECI responders in the pretreated population by prior CIDP therapy subgroup at screening are provided in Table 26. The majority of participants responded to efgartigimod PH20 SC treatment regardless of prior CIDP therapy: confirmed ECI occurred in 31 (83.8%) participants receiving prior corticosteroids, 63 (61.8%) receiving prior IVIg or SCIg. A higher percentage (31 [30.4%]) of participants in the IVIg or SCIg subgroup than in the corticosteroids (2 [5.4%])

subgroup discontinued Stage A treatment early (after they had stopped IVIg or SCIg in the run-in period and had been required to demonstrate ECMD; Section 10.1). Because week 4 was the earliest time point at which the ECI criteria could have been met, participants who discontinued treatment before week 4 (ie, before 4 treatment administrations plus 1 additional week for ECI confirmation) would not have been in the study long enough to have ECI (and to have a maximum reduction in total IgG).

Table 26: Confirmed ECI Responders by prior CIDP Therapy at screening in the pretreated population (SAF-A) (Stage A – Primary Endpoint - Subgroup analysis)

	Efgartigimod PH20 SC (N=139)	
	Corticosteroids (N=37) n (%)	IVIg or SCIg (N=102) n (%)
Number of participants with confirmed ECI (95% CI)	31 (83.8) (68.0-93.8)	63 (61.8) (51.6-71.2)
Number of participants without confirmed ECI	6 (16.2)	39 (38.2)
Completed Stage A treatment without confirmed ECI	2 (5.4)	7 (6.9)
Discontinued treatment in Stage A	4 (10.8)	32 (31.4)
Ongoing in Stage A at 88th event in Stage B	2 (5.4)	1 (1.0)
Discontinued early for other reasons	2 (5.4)	31 (30.4)

CDAS=CIDP disease activity status; CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20;IVIg=intravenous immunoglobulin; N=number of participants per treatment group/prior CIDP therapy subgroup in SAF-A; rHuPH20=recombinant human hyaluronidase PH20; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SCIg=subcutaneous immunoglobulin.
Notes: the pre-treated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾ 4 at screening. All participants in SAF-A who did not have confirmed ECI were considered ECI nonresponders. For each pior CIDP therapy subgroup, the exact 2-sided Clopper-Pearson 95% CI for the ECI responder rate is shown. The denominator for the percentage calculations was the total number of participants per prior CIDP therapy subgroup in SAF-A

Only n=3 (2.2%) participants in the pretreated population were ongoing in Stage A at the 88th event of Stage B compared to n=18 (5.6%) in the overall population. Sensitivity analysis excluding these 3 participants show similar results to those in Table 26.

ECI responders by way of deterioration in run-in

ECMD (in the run-in phase only, as no treatment-naïve participants were included) was shown by deterioration on aINCAT in n=64 out of 139 participants (46.0% of pretreated population) and of these n=40 (62.5%) had ECI during Stage A. The remaining patients in Stage A had no change in aINCAT during run (n=74, 53.2%), but demonstrated ECMD by I-RODS/mean grip strength deterioration. Of these 74 patients n = 54 had ECI (73%). This is similar to the overall population.

Secondary endpoint: Time to initial confirmed ECI in Stage A (overall and pretreated populations)

In Stage A, up to 40% of participants responded to efgartigimod PH20 SC with clinically meaningful improvement at week 4 (the earliest time point at which the ECI criteria could have been met). The median (95% CI) time to initial confirmed ECI was 43.0 (31.0-51.0) days. In the pretreated population the 4 week responder rate for ECI was 48.4% with a median time to initial confirmed ECI of 31 days (95% CI; 23-43).

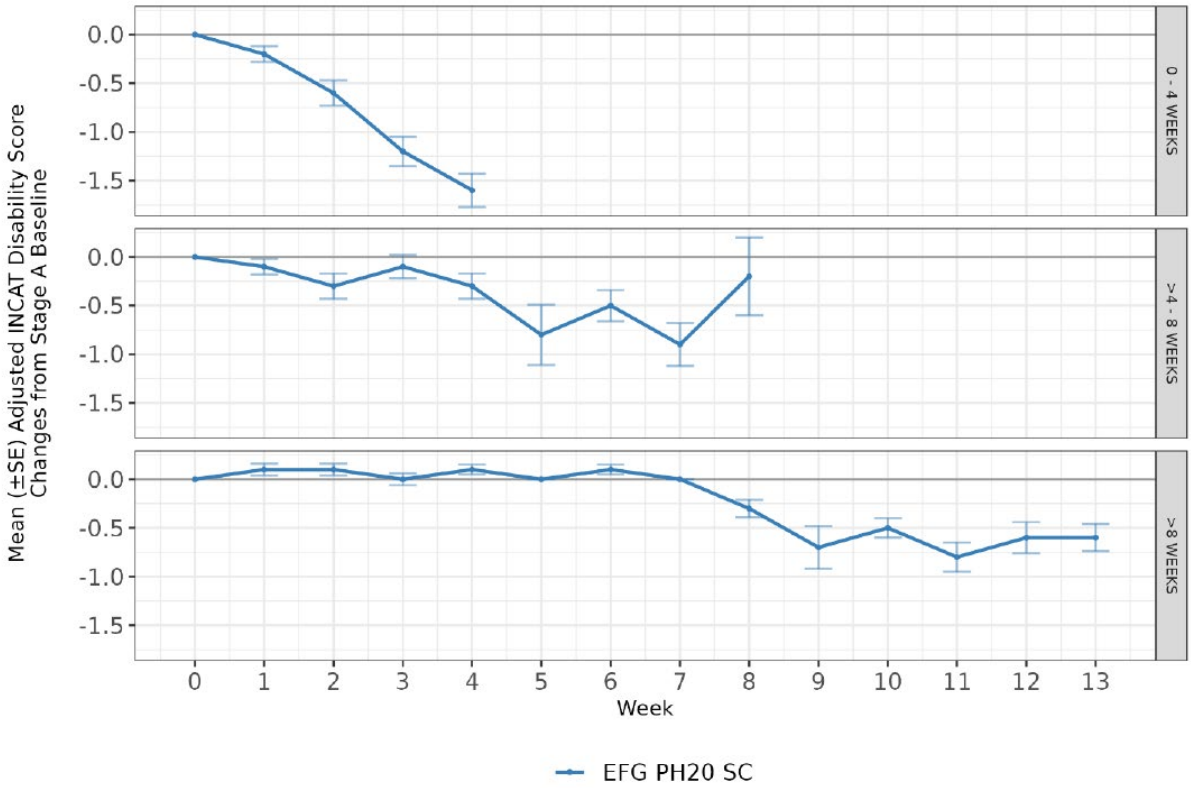
Secondary endpoint: Change from Stage A baseline in clinical scores (overall and pretreated populations)

At the last Stage A assessment, motor function and muscle strength, as assessed by mean (SD) change in aINCAT score and mean grip strength, improved consistently and with clinical relevance compared with Stage A baseline.

Table 27: Change From Stage A Baseline in aINCAT Score, I-RODS Score, and Mean Grip Strength at Stage A Last Assessment in the Pretreated Population and Overall population (Stage A – Secondary Endpoint)

	Pretreated population EFG PH20 SC (N=139)	Overall population EFG PH20 SC (N=322)
aINCAT score		
n	139	316
Mean (SD)	−1.0 (1.92)	−0.9 (1.71)
Median (min, max)	−1.0 (−8, 4)	−1.0 (−8, 6)
I-RODS score		
n	139	320
Mean (SD)	9.1 (17.12)	7.7 (15.48)
Median (min, max)	5.0 (−24, 69)	5.0 (−33, 72)
Mean grip strength – dominant hand (kPa)		
n	138	317
Mean (SD)	14.0 (19.53)	12.3 (18.68)
Median (min, max)	9.5 (−44, 79)	10.0 (−46, 79)
Mean grip strength – nondominant hand (kPa)		
n	138	317
Mean (SD)	13.3 (19.16)	11.2 (21.12)
Median (min, max)	10.0 (−44, 76)	9.0 (−83, 165)

Figure 29: aINCAT Score: Changes From Stage A Baseline Over Time by Time-on- Treatment in Stage A (SAF-A) (Stage A – Secondary Endpoint)



Efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; aINCAT=adjusted inflammatory neuropathy cause and treatment; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly)
Note: Stage A baseline was defined as the last available value before the first administration of efgartigimod PH20 SC in Stage A. The overall number of participants in each time-on-treatment group in Stage A is as follows: 0 to 4 weeks (N=165), >4 to 8 weeks (N=74), and >8 weeks (N=83).

Figure 29 represents the changes from Stage A baseline over time (mean ±SE) in aINCAT score by time-on-treatment in Stage A in the overall population. Mean changes from baseline were of greater magnitude in participants in Stage A for up to 4 weeks; however, mean improvements in these scores were evident in participants with a longer Stage A duration.

Secondary endpoint: Change from Stage A baseline in EQ-5D-5L (overall and pretreated populations)

Mean (SE) scores improved from 50.8 (1.17) at the Stage A baseline to 61.7 (1.23) at the last Stage A assessment. The mean (SE) change from the Stage A baseline to the last Stage A assessment was 10.7 (1.34). In the pretreated population Mean (SE) scores improved from 48.7 (1.85) at Stage A baseline to 61.0 (2.03) at the last Stage A assessment. The mean (SE) change from Stage A baseline to the last Stage A assessment was 12.5 (2.11).

B) STAGE B- Pivotal part of the trial.

Overall population: Primary endpoint (time to first aINCAT deterioration)

The studied period is from first dose of double-blinded IMP in Stage B (placebo or efgartigimod) and until the first aINCAT deterioration compared to Stage B. The HR for the time to clinical deterioration (increase of ≥1 point on the aINCAT score compared with Stage B baseline) comparing efgartigimod PH20 SC with placebo, estimated from a Cox proportional hazard model stratified by prior CIDP therapy and aINCAT score during Stage A, is presented in Table 28. The rate of events in the efgartigimod PH20 SC arm was statistically significantly lower than the placebo arm, with an HR of 0.394 (95% CI, 0.253-0.614) and a

p-value of 0.000039. Of the 90 events that occurred in Stage B (2 events occurred after the 88th event and before the last participant, last visit), 31 (27.9%) were reported in the efgartigimod PH20 SC arm and 59 (53.6%) in the placebo arm.

Table 28: Time to Clinical Deterioration – Cox Proportional Hazard Model (mITT Analysis Set) (Stage B – Primary Endpoint)

	Clinical deterioration (relapse) n (%)	Comparison efgartigimod PH20 SC vs placebo		
		HR	95% CI	p-value
Efgartigimod PH20 SC (N=111)	31 (27.9)	0.394	(0.253-0.614)	0.000039
Placebo (N=110)	59 (53.6)			

aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; HR=hazard ratio; IMP=investigational medicinal product; mITT=modified intent-to-treat; N=number of participants per treatment arm in the mITT analysis set; n (%)=number and percentage of participants with events of clinical deterioration (relapse) per treatment arm; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The denominator for the percentage calculations was the total number of participants per treatment arm in the mITT analysis set. The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during Stage A.

The Kaplan-Meier analysis for the time to clinical deterioration demonstrates that the participants in the efgartigimod PH20 SC arm had a lower probability for clinical deterioration than the participants in the placebo arm. The median (95% CI) time to clinical deterioration could not be calculated for the efgartigimod PH20 SC arm because less than 50% of the participants had clinically deteriorated. The median (95% CI) time to clinical deterioration in the placebo arm was 140.0 (75.0 to NC) days. The estimated percentage (95% CI) of clinical deterioration at week 24 was 26.2% (18.6-36.2) and 54.3% (44.8-64.4) in the efgartigimod PH20 SC and placebo arms, respectively, and at week 48 was 34.0% (24.9-45.2) and 59.8% (50.0-69.9), respectively (Table 29).

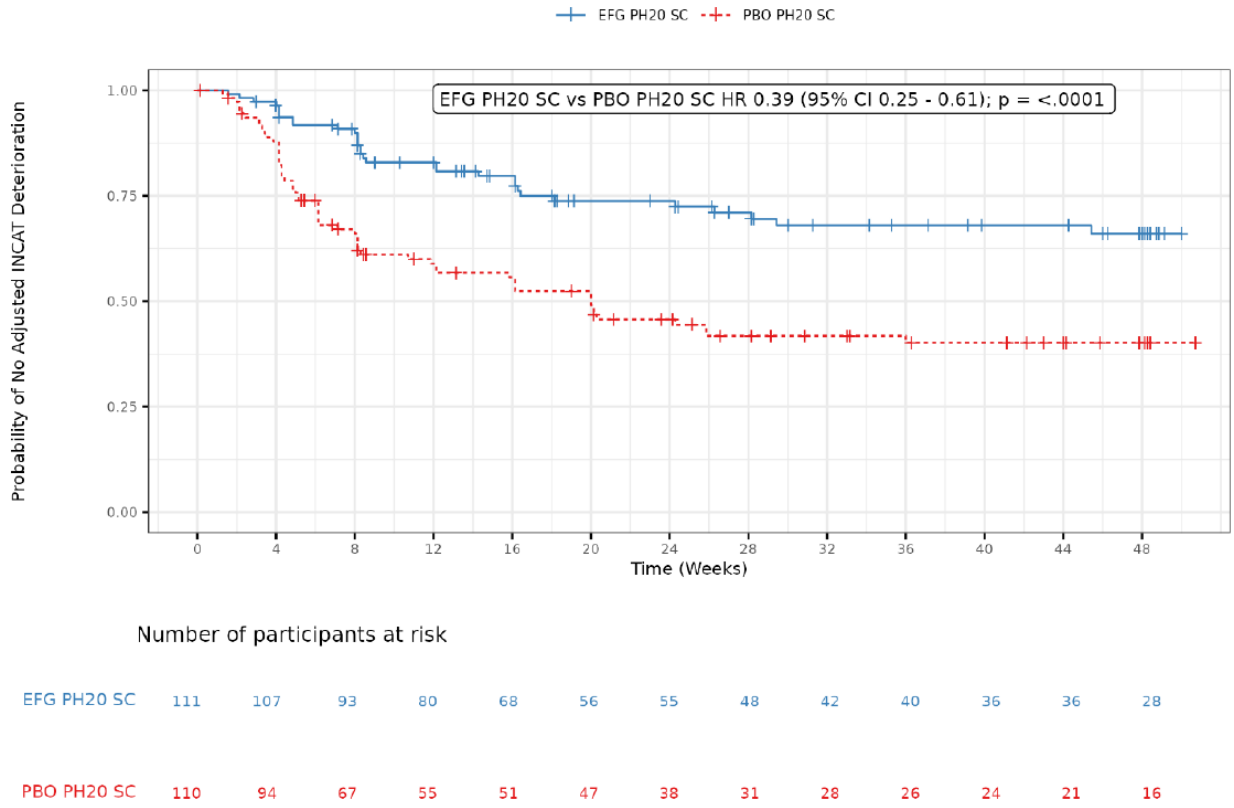
Table 29: Kaplan-Meier Estimates of the Time to Clinical Deterioration (mITT Analysis Set) (Stage B – Primary Endpoint)

	Efgartigimod PH20 SC (N=111)	Placebo (N=110)
Time to first aINCAT deterioration (days)		
25th percentile (95% CI)	115.0 (60.0 to NC)	36.0 (29.0 to 56.0)
50th percentile (95% CI)	NC (NC)	140.0 (75.0 to NC)
75th percentile (95% CI)	NC (NC)	NC (NC)
Number assessed	111	110
Number of events	31 (27.9%)	59 (53.6%)
Number censored	80 (72.1%)	51 (46.4%)

Completed Stage B treatment without aINCAT deterioration	33 (29.7%)	18 (16.4%)
Discontinued from treatment in Stage B	47 (42.3%)	33 (30.0%)
Ongoing in Stage B at 88th event in Stage B	35 (31.5%)	24 (21.8%)
Discontinued early for other reasons	12 (10.8%)	9 (8.2%)

aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; mITT=modified intent-to-treat; N=number of participants per treatment arm in the mITT analysis set; NC=not calculated; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The percentages of aINCAT deterioration at week 24 and week 48 are estimated from the Kaplan-Meier model, which accounts for censoring. The denominator for the percentage calculations was the total number of participants per treatment arm in the mITT analysis set.

Figure 30: Kaplan-Meier Plot of the Time to Clinical Deterioration (mITT Analysis Set) (Stage B – Primary Endpoint)



aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; mITT=modified intent-to-treat; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either: an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment.

Pretreated population: Primary endpoint

The rate of events in the efgartigimod PH20 SC arm was lower than in the placebo arm, with an HR of 0.269 (95% CI, 0.138-0.523) and a nominal p-value of 0.0001. This equates to a 73% reduction in the risk of relapse. Of the 45 events in Stage B, 13 (27.1%) were reported in the efgartigimod PH20 SC arm and 32 (68.1%) in the placebo arm (Table 30).

Table 30: Time to Clinical Deterioration in the pre-treated population– Cox Proportional Hazard Model (mITT Analysis Set) (Stage B – Primary Endpoint)

	Clinical deterioration (relapse) n (%)	Comparison efgartigimod PH20 SC vs placebo		
		HR	95% CI	nominal p-value
Efgartigimod PH20 SC (N=48)	13 (27.1)	0.269	(0.138-0.523)	0.0001
Placebo (N=47)	32 (68.1)			

aINCAT=adjusted inflammatory neuropathy cause and treatment; CDAS=CIDP disease activity status; CIDP= chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; HR=hazard ratio; IMP=investigational medicinal product; mITT=modified intent-to-treat; N=number of participants per treatment arm in the mITT analysis set; n (%)=number and percentage of participants with events of clinical deterioration (relapse) per treatment arm; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The denominator for the percentage calculations was the total number of participants per treatment arm in the mITT analysis set. The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during Stage A.

The Kaplan-Meier analysis for the time to clinical deterioration shows that participants in the efgartigimod PH20 SC arm had a lower probability for clinical deterioration than participants in the placebo arm. The median (95% CI) time to clinical deterioration could not be calculated for the efgartigimod PH20 SC arm because less than 50% of the participants had clinically deteriorated. The median (95% CI) time to clinical deterioration in the placebo arm was 56.0 (34.0-140.0) days. The estimated percentage (95% CI) of clinical deterioration at week 24 was 24.5% (13.9-41.1) and 71.9% (57.6-84.7) in the efgartigimod PH20 SC and placebo arms, respectively, and at week 48 was 36.4% (22.3-55.7) and 75.9% (61.2-88.3), respectively.

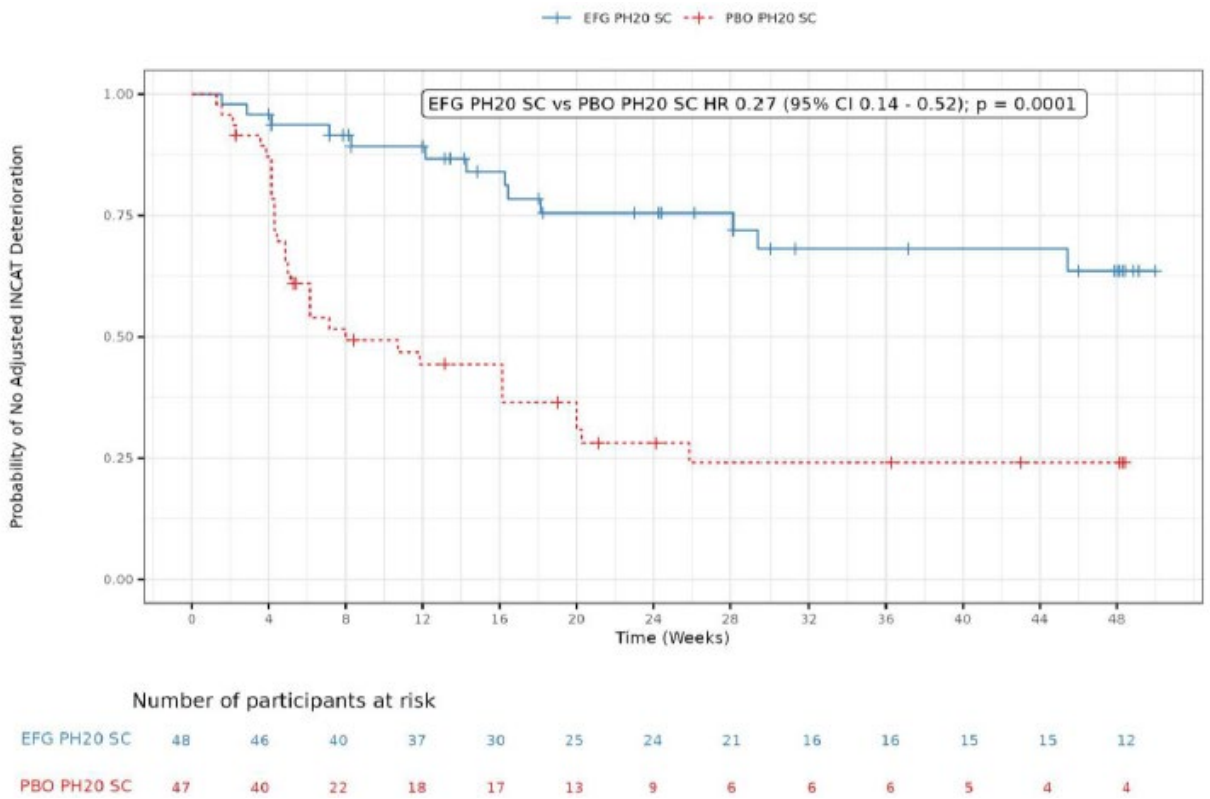
Table 31: Kaplan-Meier Estimates of the Time to Clinical Deterioration in the pre-treated population (mITT Analysis Set) (Stage B – Primary Endpoint)

	Efgartigimod PH20 SC (N=48)	Placebo (N=47)
Time to first aINCAT deterioration (days)		
25th percentile (95% CI)	197.0 (85.0 to NC)	30.0 (27.0 to 36.0)
50th percentile (95% CI)	NC (206.0 to NC)	56.0 (34.0 to 140.0)
75th percentile (95% CI)	NC (NC)	181.0 (113.0 to NC)
Estimated percentage of aINCAT deterioration at week 24 (95% CI)	24.5 (13.9 to 41.1)	71.9 (57.6 to 84.7)
Estimated percentage of aINCAT deterioration at week 48 (95% CI)	36.4 (23.3 to 55.7)	75.9 (61.2 to 88.3)

Number assessed	48	47
Number of events	13 (27.1%)	32 (68.1%)
Number censored	35 (72.9%)	15 (31.9%)
Completed Stage B treatment without aINCAT deterioration	14 (29.2%)	4 (8.5%)
Discontinued from treatment in Stage B	21 (43.8%)	11 (23.4%)
Ongoing in Stage B at 88th event in Stage B	18 (37.5%)	8 (17.0%)
Discontinued early for other reasons	3 (6.3%)	3 (6.4%)

aINCAT=adjusted inflammatory neuropathy cause and treatment; CDAS=CIDP disease activity status; CIDP= chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; HR=hazard ratio; IMP=investigational medicinal product; mITT=modified intent-to-treat; N=number of participants per treatment arm in the mITT analysis set; n (%)=number and percentage of participants with events of clinical deterioration (relapse) per treatment arm; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The percentages of aINCAT deterioration at week 24 and week 48 are estimated from the Kaplan-Meier model, which accounts for censoring. The denominator for the percentage calculations was the total number of participants per treatment arm in the mITT analysis set.

Figure 31: Kaplan-Meier Plot of the Time to Clinical Deterioration in the pretreated population (mITT Analysis Set) (Stage B – Primary Endpoint)



aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; mITT=modified intent-to-treat; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either: an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment.

Sensitivity analyses for the primary endpoint, Stage B (overall and pretreated population)

Per protocol analysis set (overall population)

Table 32: Time to Clinical Deterioration– Cox Proportional Hazard Model (PP Analysis Set) (Stage B – Primary Endpoint - Sensitivity analysis)

	Clinical deterioration (relapse) n (%)	Comparison efgartigimod PH20 SC vs placebo		
		HR	95% CI	p-value
Efgartigimod PH20 SC (N=96)	28 (29.2)	0.369	(0.231-0.592)	<0.0001
Placebo (N=88)	51 (58.0)			

aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; HR=hazard ratio; IMP=investigational medicinal product; N=number of participants per treatment arm in the PP analysis set; n (%)=number and percentage of participants with events of clinical deterioration (relapse) per treatment arm; PP=per protocol; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The denominator for the percentage calculations was the total number of participants per treatment arm in the PP analysis set. The HR was obtained from a Cox proportional hazard model with treatment as a fixed effect, and the model was stratified by prior CIDP therapy and aINCAT score during Stage A.

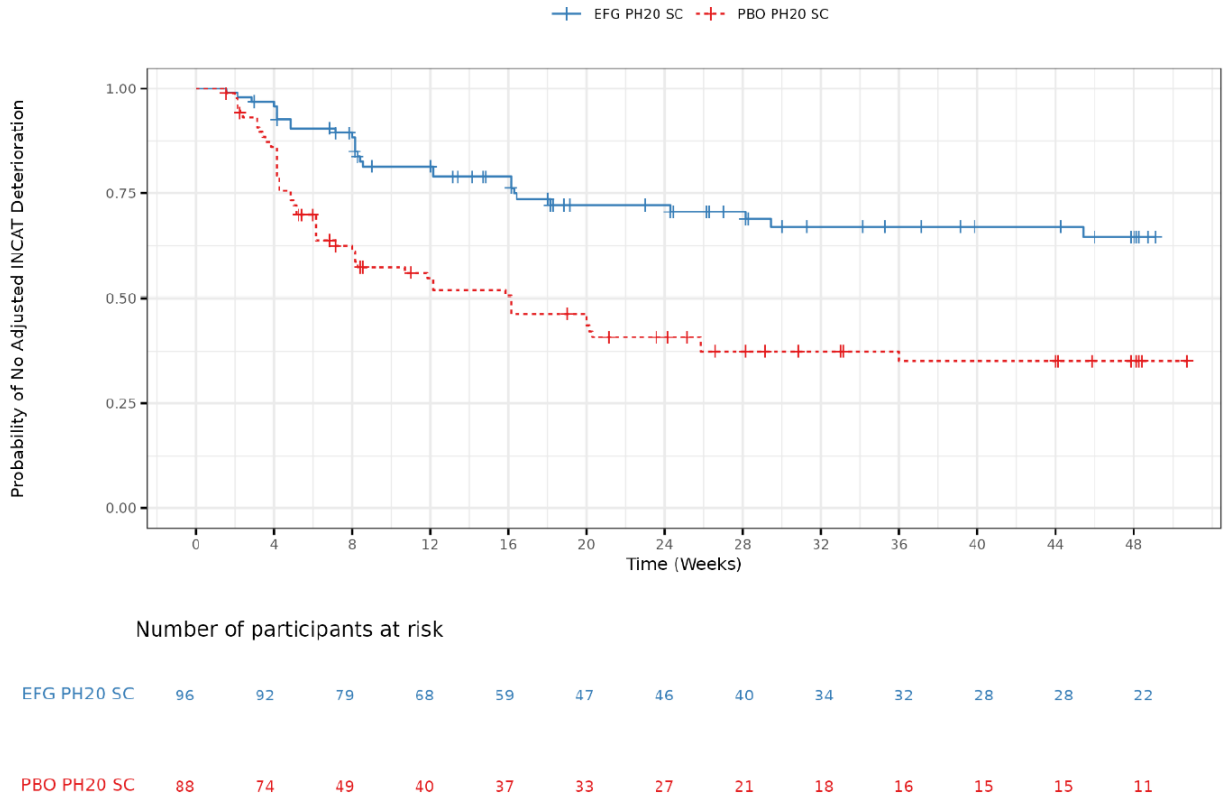
Table 33: Kaplan-Meier Estimates of the Time to Clinical Deterioration (PP Analysis Set) (Stage B – Primary Endpoint – Sensitivity Analysis)

	Efgartigimod PH20 SC (N=96)	Placebo (N=88)
Time to first aINCAT deterioration (days)		
25th percentile (95% CI)	114.0 (58.0 to 318.0)	34.0 (29.0 to 43.0)
50th percentile (95% CI)	NC (NC)	113.0 (56.0 to 181.0)
75th percentile (95% CI)	NC (NC)	NC (252.0 to NC)
Estimated percentage of aINCAT deterioration at week 24 (95% CI)	27.8 (19.5 to 38.7)	59.2 (48.5 to 70.1)
Estimated percentage of aINCAT deterioration at week 48 (95% CI)	35.5 (25.5 to 47.9)	64.9 (53.8 to 75.9)
Number assessed	96	88
Number of events	28 (29.2%)	51 (58.0%)
Number censored	68 (70.8%)	37 (42.0%)
Completed Stage B treatment without aINCAT deterioration	26 (27.1%)	12 (13.6%)
Discontinued from treatment in Stage B	42 (43.8%)	25 (28.4%)
Ongoing in Stage B at 88th event in Stage B	32 (33.3%)	20 (22.7%)
Discontinued early for other reasons	10 (10.4%)	5 (5.7%)

aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; N=number of participants per treatment arm in the PP analysis set; NC=not calculated; PP=per protocol; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first

IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment. The percentages of aINCAT deterioration at week 24 and week 48 are estimated from the Kaplan-Meier model, which accounts for censoring. The denominator for the percentage calculations was the total number of participants per treatment arm in the PP analysis set

Figure 32: Kaplan-Meier Plot of the Time to Clinical Deterioration (PP Analysis Set)(Stage B – Primary Endpoint – Sensitivity Analysis)



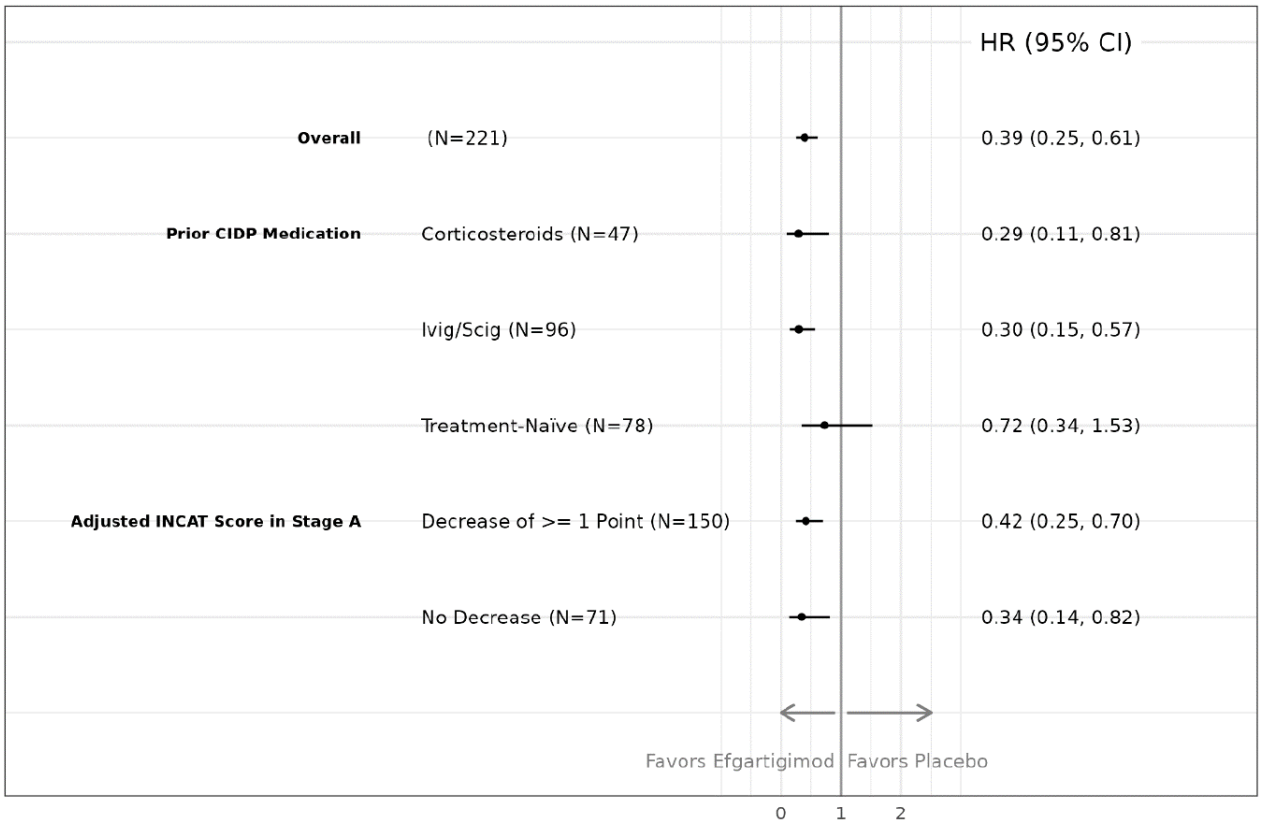
aINCAT=adjusted inflammatory neuropathy cause and treatment; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; PP=per protocol; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ≥1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ≥2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of deterioration were censored at the date of the last available aINCAT assessment.

Stratification factors (time to first occurrence of clinical deterioration)

Overall population

The HR (and 95% CI) for the time to clinical deterioration comparing efgartigimod PH20 SC with placebo, estimated from a Cox proportional hazard model overall and for the stratification factors of prior CIDP therapy and aINCAT score during Stage A, are presented in Figure 33. By prior CIDP therapy, the HR (95% CI) was 0.29 (0.11-0.81) for participants who were receiving corticosteroids, 0.30 (0.15-0.57) for participants who were receiving IVIg or SCIg, and 0.72 (0.34-1.53) for participants who were treatment-naïve at the start of the study.

Figure 33: Forest Plot of the Time to First Occurrence of Clinical Deterioration – HR (95% CI) Overall and by Subgroups (mITT Analysis Set) (Stage B – Primary Endpoint – Subgroup Analysis)



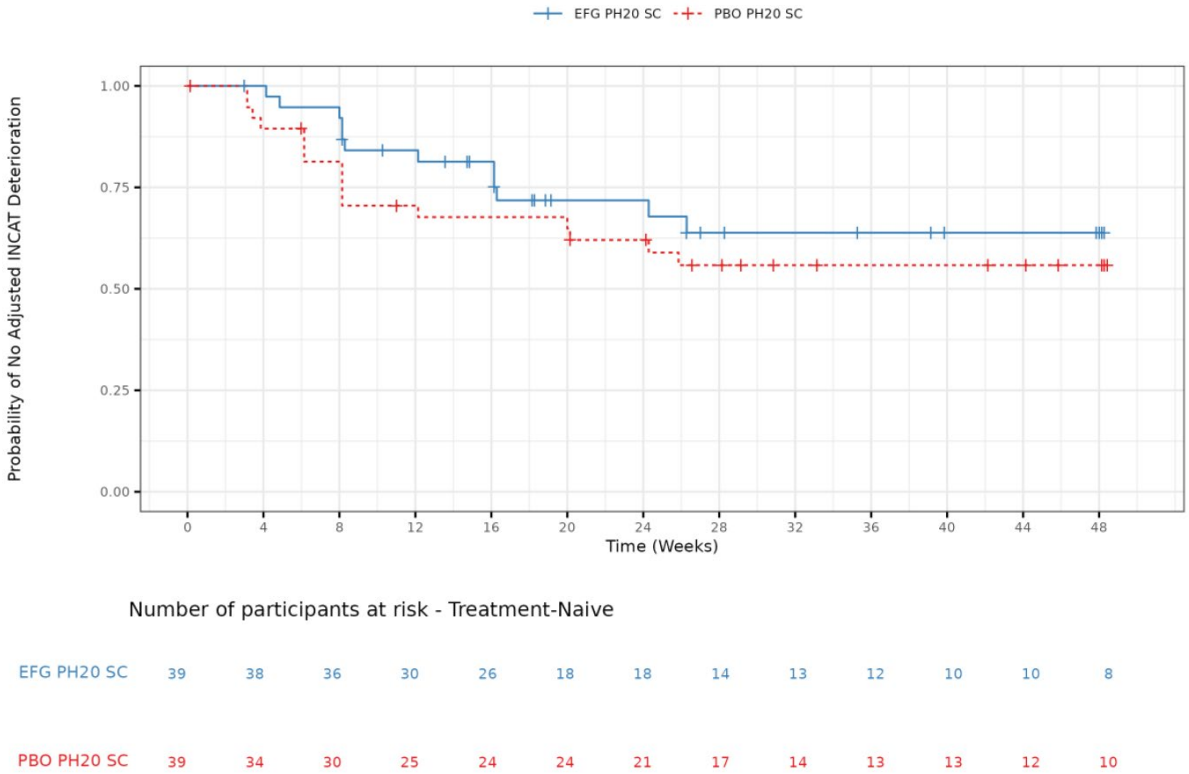
INCAT=inflammatory neuropathy cause and treatment; CIDP=chronic inflammatory demyelinating polyneuropathy; HR=hazard ratio; IVIg=intravenous immunoglobulin; mITT=modified intent-to-treat; SCIg=subcutaneous immunoglobulin
Note: Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥6 months before screening. The HRs were obtained from a Cox proportional hazard model.

Table 34: Clinical Deterioration Rates Overall and by Stratification Factors (mITT Analysis Set) (Stage B – Primary Endpoint – Subgroup Analysis)

	Efgartigimod PH20 SC n/N (%)	**Placebo n/N (%)**
Overall	31/111 (27.9)	59/110 (53.6)
Prior CIDP therapy		
Corticosteroids	5/24 (20.8)	15/23 (65.2)
IVIg or SCIg	14/48 (29.2)	28/48 (58.3)
Treatment-naïve	12/39 (30.8)	16/39 (41.0)
aINCAT Score during Stage A		
aINCAT score decrease of ≥1 point during Stage A	24/75 (32.0)	41/75 (54.7)
No decrease in aINCAT score during Stage A	7/36 (19.4)	18/35 (51.4)

aINCAT=adjusted inflammatory neuropathy cause and treatment; CIDP=chronic inflammatory demyelinating polyneuropathy; IVIg=intravenous immunoglobulin; mITT=modified intent-to-treat; n=number of participants with clinical deterioration per subgroup; N=number of participants per subgroup in the mITT; SCIg=subcutaneous immunoglobulin
Note: Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ⩾6 months before screening

Figure 34: Kaplan-Meier Plot of the Time to Clinical Deterioration by Prior CIDP Therapy Subgroup (Treatment-Naïve) at Screening (mITT Analysis Set) (Stage B – Primary Endpoint – Subgroup Analysis)

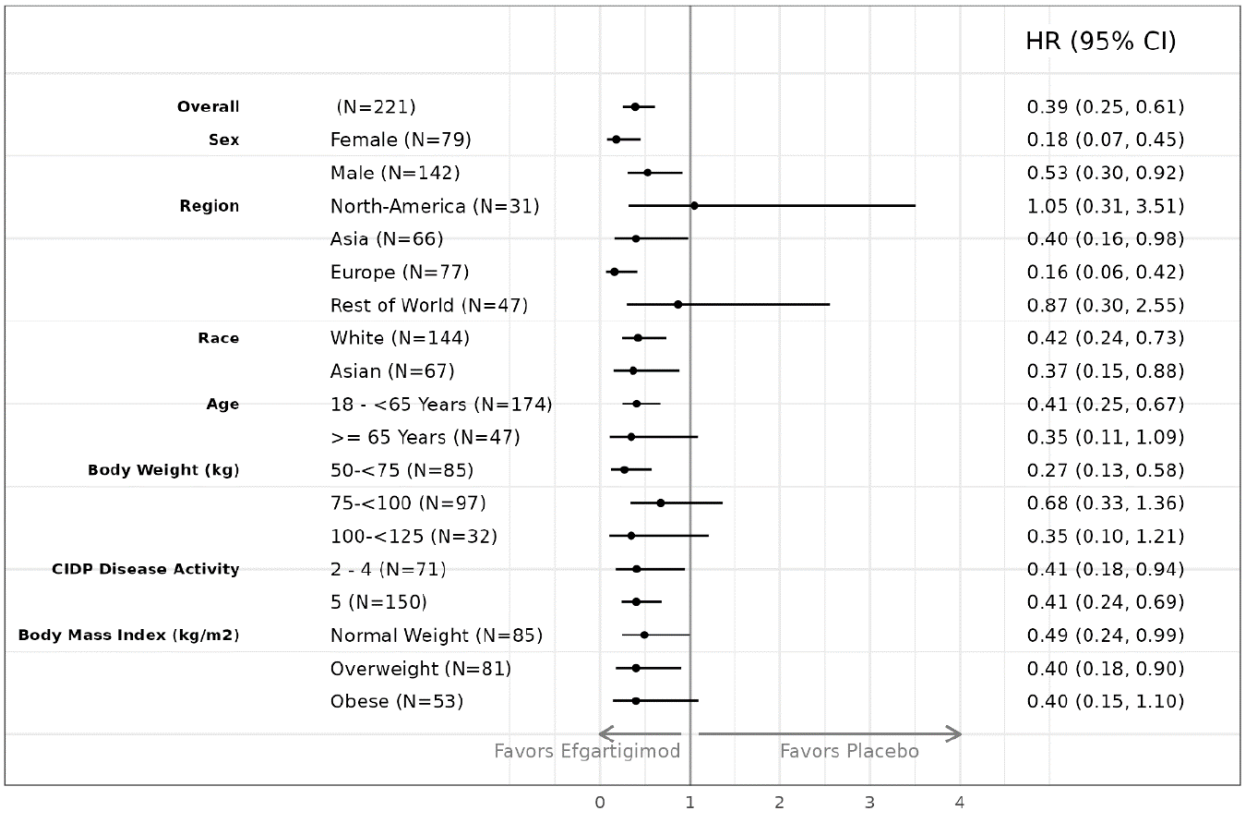


CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; INCAT=inflammatory neuropathy cause and treatment; mITT=modified intent-to-treat; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: The time to clinical deterioration is defined as the time in days from the first IMP administration in Stage B to the first occurrence of either an increase in aINCAT score of ⩾1 point compared with Stage B baseline if confirmed at the next visit or an increase in aINCAT score of ⩾2 points compared with Stage B baseline. Stage B baseline corresponds to the last available value before the first IMP administration in Stage B. Participants who completed Stage B or discontinued treatment in Stage B before the first occurrence of clinical deterioration were censored at the date of the last available aINCAT assessment.

Other sensitivity analyses of primary endpoint (overall population shown)

The HR (and 95% CI) of the time to clinical deterioration comparing efgartigimod PH20 SC to placebo, estimated from a Cox proportional hazard model overall and for all subgroups, are shown in Figure 35. In most subgroups, the effect of efgartigimod PH20 SC was consistent and similar to the overall effect. Regional subgroups of North America and ROW have few participants (N=31 and N=47, respectively, resulting in broad and inconclusive CIs and overlap with the other regions. Furthermore, demographic factors associated with those regions (including ethnicity, body weight, and BMI) have consistency in point estimates. Additionally, consistently high ECI response rates were observed across the regions in Stage A. Therefore, these observations were most likely due to small sample sizes and statistical variability, and not to true regional effects.

Figure 35: Forest Plot of the Time to First Occurrence of Clinical Deterioration – HR (95% CI) Overall and by Subgroups (mITT Analysis Set) (Stage B – Primary Endpoint – Subgroup Analysis)



CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; EEA=European Economic Area; EFTA=European Free Trade Association; EU=European Union; HR=hazard ratio; mITT=modified intent-to-treat; ROW=rest of world; UK=United Kingdom; US=United States
Notes: North America (US, Canada); Asia (China, Japan, Taiwan); Europe (EU, UK, EEA, EFTA countries); and ROW (including Ukraine, Russian Federation, Georgia, Israel, Serbia, Turkey)

Response in Stage A and time to clinical deterioration in Stage B

No clinically meaningful differences were observed by aINCAT score in Stage A (decrease of ≥1 point vs no decrease), suggesting that the time to first occurrence of clinical deterioration in Stage B was not dependent on aINCAT improvement in Stage A (pretreated and overall population).

Secondary endpoint: Time to CIDP progression (I-RODS)

The HR for the time to CIDP disease progression (defined as the time from the first dose of double-blinded IMP to the first I-RODS score decrease ≥4 points compared with Stage B baseline using the centile metric) comparing efgartigimod PH20 SC with placebo, estimated from a Cox proportional hazard model stratified by prior CIDP therapy and aINCAT score during Stage A, is presented below for the overall and pretreated population.

Table 35: Event rates (I-RODS score decrease ⩾4 points compared with Stage B baseline using the centile metric)

Descriptive statistics and estimate variability	**Time to CIDP Disease Progression – Cox Proportional Hazard Model (mITT Analysis Set)**				
	Treatment group	Pretreated population EFG PH20 SC	Pretreated population Placebo	Overall population EFG PH20 SC	Overall population Placebo
	Number of subjects	48	47	111	110
	CIDP disease progression n (%)	18 (37.5)	31 (66.0)	40 (36.0)	57 (51.8)

Effect estimate per comparison	Secondary endpoint	Comparison groups	EFG PH20 SC vs placebo
		HR	Pretreated population: 0.400 Overall population: 0.537
		95% CI	Pretreated population: (0.218-0.734) Overall population: (0.354-0.814)
		Nominal p-value	Pretreated population: 0.0031 Overall population: 0.0034

Secondary endpoint: Improved functional level compared to Stage B baseline (I-RODS)

The odds ratio (exact 2-sided 95% CI) for improved functional level (ie, the participant had at least 1 Stage B I-RODS assessment with an increase of ≥4 points), comparing efgartigimod PH20 SC with placebo, in the overall population, was 1.441 (95% CI, 0.814-2.567; nominal p-value=0.2294). In the pretreated population the OR was 2.433 (95% CI 0.961-6.432; nominal p-value=0.0621).

Secondary endpoint: Change from Stage B baseline in clinical scores

In the efgartigimod PH20 SC arm, motor function and muscle strength, based on mean (SD) change in aINCAT score and mean grip strength, remained stable from Stage B baseline to the last Stage B assessment. In the placebo arm, motor function and muscle strength worsened by the last Stage B assessment compared with Stage B baseline.

Table 36: *Change from Stage B baseline in clinical scores*

Change from Stage B Baseline in aINCAT Score, I-RODS Score, Mean Grip Strength, MRC Sum Score, and TUG Score at Last Assessment (mITT Analysis Set)				
Treatment group	Pretreated population EFG PH20 SC	Pretreated population Placebo	Overall population EFG PH20 SC	Overall population Placebo
Number of subjects	48	47	111	110
aINCAT score				
n	48	47	111	109
Mean (SD)	0.0 (1.12)	1.5 (2.08)	0.1 (1.08)	0.9 (1.98)
Median (min, max)	0.0 (−3, 2)	1.0 (−2, 9)	0.0 (−3, 2)	1.0 (−5, 9)
I-RODS score				
n	48	47	111	108
Mean (SD)	1.3 (10.82)	−13.5 (21.50)	0.8 (12.33)	−7.0 (19.10)
Median (min, max)	0.0 (−22, 27)	−7.0 (−81, 20)	0.0 (−52, 45)	−3.0 (−81, 45)
Mean grip strength – dominant hand (kPa)				
n	48	47	111	109
Mean (SD)	2.4 (13.71)	−14.3 (21.27)	2.1 (13.29)	−8.2 (20.69)
Median (min, max)	1.5 (−31, 39)	−11.0 (−71, 41)	2.0 (−31, 39)	−5.0 (−71, 45)
Mean grip strength – nondominant hand (kPa)				
n	48	47	111	109
Mean (SD)	3.5 (13.92)	−12.4 (23.16)	2.0 (17.33)	−6.9 (21.30)
Median (min, max)	1.0 (−26, 41)	−7.0 (−80, 40)	1.0 (−111, 41)	−4.0 (−80, 47)
MRC sum score (Mean (SE))	−0.5 (0.71)	−5.7 (1.64)	−0.3 (0.43)	−3.0 (0.86)
TUG test (Mean (SE)) (seconds)	0.6 (0.46)	2.9 (0.98)	0.8 (0.36)	1.9 (0.60)

Secondary endpoint: Change from Stage A baseline in clinical scores

Table 37: Change from Stage A baseline in clinical scores

Change from Stage A Baseline in aINCAT Score, I-RODS Score, Mean Grip Strength, MRC Sum Score, and TUG Score at Last Assessment				
Treatment group	Pretreated population EFG PH20 SC	Pretreated population Placebo	Overall population EFG PH20 SC	Overall population Placebo
aINCAT score				
n	48	47	110	109
Mean (SD)	−1.6 (2.30)	−0.1 (2.02)	−1.3 (1.86)	−0.4 (1.85)
Median (min, max)	-1.0 (-8; 1)	0.0 (-5; 4)	-1.0 (-8; 2)	0.0 (-6; 4)
I-RODS score				
n	48	47	111	107
Mean (SD)	15.4 (23.58)	2.3 (15.31)	13.5 (21.38)	5.0 (14.35)
Median (min, max)	6.5 (-28; 81)	3.0 (-57; 48)	7.0 (-45; 81)	4.0 (-57; 55)
Mean grip strength – dominant hand (kPa)				
n	48	47	111	109
Mean (SD)	22.3 (22.72)	6.4 (19.90)	19.4 (21.91)	9.2 (19.98)
Median (min, max)	15.0 (-6; 95)	3.0 (-53; 64)	14.0 (-19; 95)	6.0 (-53; 67)
Mean grip strength – nondominant hand (kPa)				
n	48	47	111	109
Mean (SD)	22.7 (22.56)	7.3 (20.95)	19.2 (22.71)	9.6 (20.13)
Median (min, max)	17.0 (-9; 88)	3.0 (-51; 74)	12.0 (-13; 91)	5.0 (-51; 74)
MRC sum score (Mean (SE))	6.8 (8.76)	0.4 (8.48)	5.6 (7.40)	2.7 (7.67)
TUG test (Mean (SE)) (seconds)	-6.0 (9.41)	-0.5 (17.11)	-4.9 (7.14)	-4.3 (16.56)

Secondary endpoint: Time to 10% decrease in I-RODS during Stage B

The median (95% CI) time to a 10% decrease in the I-RODS score could not be calculated for participants in the efgartigimod PH20 SC arm (260.0 to NC) and was 111 days (84.0 to NC) in the placebo arm. The Kaplan-Meier estimated percentage (95% CI) of time to 10% decrease in the I-RODS score at week 24 was 29.0% (21.0-39.2) and 50.2% (40.2-61.1) in the efgartigimod PH20 SC and placebo arm, respectively, and at week 48 was 40.4% (30.0-52.7) and 59.0% (47.5-70.9), respectively. This pattern was similar in the pretreated population.

Secondary endpoint: Change from Stage B baseline in EQ-5D-5L

The mean (SE) change from Stage B baseline to the last assessment was 0.5 (1.77) in the efgartigimod PH20 SC arm and −10.2 (2.47) in the placebo arm.

Table 38: EQ-5D-5L Visual analogue scale Scores Changes from Stage B Baseline Over Time (SAF-B) (Stage B – Secondary Endpoint)

	Efgartigimod PH20 SC (N=111)		Placebo (N=110)	
	n	Mean (SE)	n	Mean (SE)
Baseline Stage B	99	66.9 (1.68)	96	65.6 (1.89)
Week 12	69	2.9 (1.48)	49	−0.6 (2.34)
Week 24	46	5.7 (1.88)	30	2.5 (2.85)
Week 36	36	4.4 (2.58)	22	1.1 (2.75)
Week 48	29	9.0 (2.78)	14	11.1 (3.83)
Last assessment Stage B	97	0.5 (1.77)	90	−10.2 (2.47)

efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per treatment arm in the Stage B analysis set; n=number of participants with improved functional level per arm; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly);

In the pretreated population the mean (SE) change from Stage B baseline to the last assessment was 3.1 (2.42) in the efgartigimod PH20 SC arm and −18.6 (4.05) in the placebo arm.

Exploratory endpoint: Change from Stage B baseline in other PROs (overall population only)

BPI-SF: Participants rate pain severity and pain interference on a scale from 0 to 10, with lower scores indicating less pain severity or pain interference. The mean (SE) changes from Stage B baseline in pain severity scores to the last assessment were −0.17 (0.148) and 0.44 (0.191) in the efgartigimod PH20 SC and placebo arms, respectively. The mean (SE) changes in pain interference scores were −0.09 (0.170) and 0.55 (0.183) in the efgartigimod PH20 SC and placebo arms, respectively. Results were similar in the pretreated population.

TSQM-9: Each TSQM-9 domain score ranges from 0 to 100, with higher scores representing greater satisfaction with CIDP treatment received. At Stage B baseline, mean (SE) global satisfaction was 65.9 (1.94) and 69.8 (1.88) for the efgartigimod PH20 SC and placebo arms, respectively. At the last Stage B assessment, global satisfaction was 66.1 (2.26) and 65.3 (2.25) in the efgartigimod PH20 SC and placebo arms, respectively. Stratified for prior CIDP treatment mean (SE) global satisfaction with their current treatment at the run-in visit was numerically lower (59.3 (3.23) for IVIg/SCIg, 56.0 (5.22) for corticosteroids and 49.0 (5.15) for treatment-naïve). Results were similar in the pretreated population.

RT-FSS: Scores range from 0 to 21, with higher scores indicating greater fatigue severity. The mean (SE) change in the total score from Stage B baseline to the last assessment was 0.0 (0.57) and 0.5 (0.53) in the efgartigimod PH20 SC and placebo arms, respectively. In the pretreated population, the mean (SE) change in the total score from Stage B baseline to the last assessment was −1.3 (0.86) and 1.1 (0.72) in the efgartigimod PH20 SC and placebo arms, respectively. Results were similar in the pretreated population.

HADS: Scores range from 0 to 21, with higher scores indicating greater levels of anxiety or depression. The mean (SE) change in the total anxiety score from Stage B baseline to the last assessment was −0.1 (0.26) in the efgartigimod PH20 SC arm and 0.6 (0.32) in the placebo arm. The mean (SE) change in total depression score from Stage B baseline to the last assessment was −0.2 (0.31) in the efgartigimod PH20 SC arm and 0.7 (0.35) in the placebo arm. Results were similar in the pretreated population.

PGIC: At the last Stage B assessment, most participants in both arms reported a global impression of change as "very much better," "much better," or "a little better." In the efgartigimod PH20 SC arm, the percentage of participants reporting improvement was: 22.0%, "very much better"; 29.4%, "much better"; 25.7%, "a little better"

In the placebo arm, the percentage of participants reporting improvement was: 11.3%, "very much better"; 27.8%, "much better"; 22.7%, "a little better"

In the pretreated population, active arm, results were similar. In the pretreated placebo arm fewer patients (around 32%) were "very much better" or "much better".

Ancillary analyses

None

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 39: Summary of Efficacy for trial ARGX-113-1802 Stage A and B

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)		
Study identifier	Study Number: ARGX-113-1802 IND 143294 EudraCT number 2019-003076-39 NCT04281472	
Design	Phase 2, prospective, multisite study in 2 stages: Stage A: open-label Stage B: randomized- withdrawal, double- blinded, PBO- controlled The total study duration for each participant was up to 80 weeks, with a maximum cumulative treatment period of 61 weeks.	
	Duration of screening: Duration of main phase: Duration of run-in phase:	Up to 28 days Stage A (open-label): up to 12 weeks (with an optional additional week) Stage B (double-blinded, randomised-withdrawal): up to 48 weeks Up to 12 weeks
	Duration of extension phase:	Follow-up: 28 days after the final dose of IMP (if the participant did not roll over to the OLE study, ARGX-113-1902)
Hypothesis	Superiority (Time to first adjusted INCAT deterioration compared to Stage B baseline (clinical deterioration)	

Treatments groups	efgartigimod alfa subcutaneous (EFG PH20 SC)		Stage A (open label): EFG PH20 SC once weekly, up to 12 weeks (with an optional additional week for ECI confirmation), with a minimum of 4 administrations Participants remained in Stage A until ECI was confirmed at 2 consecutive visits. Participants who had ECI at 2 consecutive visits during Stage A entered Stage B (pretreated population N=139; overall population N=322) Stage B (double-blinded, randomised-withdrawal): EFG PH20 SC once weekly, up to 48 weeks (pretreated population N= 48;overall N=111)
	Placebo		Stage B (double-blinded, randomised-withdrawal): Placebo once weekly, up to 48 weeks (pretreated population N= 47; overall N=110)
Endpoints and definitions **Stage A** (open label)	Primary endpoint	Activity of efgartigimod PH20 SC based on the percentage of participants classified as treatment responders	Percentage of participants with confirmed evidence of clinical improvement (ECI) during Stage A (ECI responders)
	Secondary endpoint	Time to clinical improvement	Time to initial ECI during Stage A
Endpoints and definitions **Stage B** (double-blinded, randomised-withdrawal period)	Primary endpoint	Efficacy of efgartigimod PH20 SC compared to placebo based on the time needed for the first evidence of clinical deterioration	Time to first aINCAT deterioration (defined by the time from the first dose of double-blinded IMP to the first aINCAT deterioration compared to Stage B baseline)
	Secondary endpoint	Efficacy of efgartigimod PH20 SC compared to placebo	Time to CIDP disease progression (defined as the time from the first dose of double-blinded IMP to the first I-RODS score decrease ⩾4 points compared to Stage B baseline using the centile metric)
Database lock	08 August 2023		

Results and Analysis

Analysis description	**Primary Analysis - Stage A (open-label):** Percentage of participants with confirmed evidence of clinical improvement (ECI) during Stage A (ECI responders)

<table>
<tr><td>Analysis population and time point description</td><td colspan="3">Confirmed ECI Responders in the Pre-treated and Overall Population</td></tr>
<tr><td rowspan="5">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Pretreated population, EFG PH20 SC</td><td>Overall population, EFG PH20 SC</td></tr>
<tr><td>Number of subjects</td><td>139</td><td>322</td></tr>
<tr><td>Number of participants with confirmed ECI n (%)</td><td>94 (67.6)</td><td>214 (66.5)</td></tr>
<tr><td>Exact 2-sided Clopper Pearson 95% CI</td><td>59.2-75.3</td><td>61.0-71.6</td></tr>
<tr><td colspan="3"><u>Pre-treated population:</u>
The pretreated population includes participants who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening. All participants in SAF-A who did not have confirmed ECI were considered ECI nonresponders, including participants ongoing in Stage A at the occurrence of the 88th event in Stage B. The denominator for the percentage calculations was the total number of participants in SAF-A.
<u>Overall population:</u>
All participants in SAF-A who did not have confirmed ECI were considered ECI nonresponders, including participants ongoing in Stage A at the occurrence of the 88th event. The denominator for the percentage calculations was the total number of participants in SAF-A.</td></tr>
<tr><td rowspan="2">Effect estimate per comparison</td><td rowspan="2">Primary endpoint</td><td>Comparison groups</td><td>NA</td></tr>
<tr><td>P-value</td><td>NA</td></tr>
<tr><td>Notes</td><td colspan="3">Discontinued treatment in Stage A:
Pretreated: 41 (29.5), overall: 93 (28.9)
Ongoing in Stage A at 88th event in Stage B:
Pretreated: 3 (2.2); overall: 18 (5.6)</td></tr>
<tr><td>Analysis description</td><td colspan="3">Secondary analysis – Stage A (open-label):
Time to initial confirmed ECI during Stage A; pre-specified</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Pre-treated and overall population</td></tr>
</table>

Descriptive statistics and estimate variability		Pretreated population EFG PH20 SC (N=139)	Overall population EFG PH20 SC (N=322)
	Time to initial confirmed ECI (days)		
	25th percentile (95% CI) (days)	22.0 (NC)	22.0 (22.0-23.0)
	50th percentile (95% CI) (days)	31.0 (23.0-43.0)	43.0 (31.0-51.0)
	75th percentile (95% CI) (days)	70.0 (57.0-78.0)	71.0 (70.0-78.0)
	Estimated percentage of confirmed ECI at week 12 (95% CI)	90.1 (81.2-95.9)	90.0 (84.4-94.2)
	Number assessed	139	322
	Number of events	94 (67.6%)	214 (66.5%)
	Number censored	45 (32.4%)	108 (33.5%)
	Completed Stage A treatment without confirmed ECI	9 (6.5%)	21 (6.5%)
	Discontinued treatment in Stage A	36 (25.9%)	87 (27.0%)
	Ongoing in Stage A at 88th event in Stage B	3 (2.2%)	18 (5.6%)
	Discontinued early for other reasons	33 (23.7%)	69 (21.4%)

<table>
<tr><td>Analysis description</td><td colspan="5">Primary Analysis – Stage B (randomised-withdrawal, double-blinded, placebo-controlled)
Time to first aINCAT deterioration (defined by the time from the first dose of double-blinded IMP to the first aINCAT deterioration compared to Stage B baseline)</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="5">Intent to treat</td></tr>
<tr><td rowspan="5">Descriptive statistics and estimate variability</td><td colspan="5">Time to Clinical Deterioration – Cox Proportional Hazard Model (mITT Analysis Set) (Stage B – Primary Endpoint)</td></tr>
<tr><td>Treatment group</td><td>Pretreated population
EFG PH20 SC</td><td>Pretreated population
Placebo</td><td>Overall population
EFG PH20 SC</td><td>Overall population
Placebo</td></tr>
<tr><td>Number of subjects</td><td>48</td><td>47</td><td>111</td><td>110</td></tr>
<tr><td>Clinical deterioration (relapse) n(%)</td><td>13 (27.1)</td><td>32 (68.1)</td><td>31 (27.9)</td><td>59 (53.6)</td></tr>
<tr><td colspan="5"></td></tr>
<tr><td>Effect estimate per comparison</td><td>Primary endpoint</td><td>Comparison groups</td><td colspan="3">EFG PH20 SC vs placebo</td></tr>
<tr><td></td><td>HR</td><td colspan="3">Pretreated population: 0.269
Overall population:
0.394</td></tr>
<tr><td></td><td>95% CI</td><td colspan="3">Pretreated population: (0.138-0.523)
Overall population:
(0.253-0.614)</td></tr>
<tr><td></td><td>p-value for mITT</td><td colspan="3">Pretreated population: 0.0001
Overall population:
0.000039</td></tr>
<tr><td>Notes</td><td></td><td colspan="4">Censored participants - Discontinuation from treatment in Stage B
<u>Pretreated population:</u>
EFG PH20 SC 21 (43.8%)
Placebo 11 (23.4%)
<u>Overall population:</u>
EFG PH20 SC 47 (42.3%)
Placebo 33 (30.0%)

Ongoing in Stage B at 88th event in Stage B
<u>Pretreated population:</u>
EFG PH20 SC 18 (37.5%)
Placebo 8 (17.0%)</td></tr>
</table>

		Overall population: EFG PH20 SC 35 (31.5%) Placebo 24 (21.8%)			
Analysis description	**Secondary analysis – Stage B (randomised-withdrawal, double-blinded, placebo-controlled):** Time to CIDP disease progression (defined as the time from the first dose of double-blinded IMP to the first I-RODS score decrease ⩾4 points compared to Stage B baseline using the centile metric)				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability	**Time to CIDP Disease Progression – Cox Proportional Hazard Model (mITT Analysis Set)**				
	Treatment group	Pretreated population EFG PH20 SC	Pretreated population Placebo	Overall population EFG PH20 SC	Overall population Placebo
	Number of subjects	48	47	111	110
	CIDP disease progression n (%)	18 (37.5)	31 (66.0)	40 (36.0)	57 (51.8)
Effect estimate per comparison	Secondary endpoint	Comparison groups		EFG PH20 SC vs placebo	
		HR		Pretreated population: 0.400 Overall population: 0.537	
		95% CI		Pretreated population: (0.218-0.734) Overall population: (0.354-0.814)	
		Nominal p-value		Pretreated population: 0.0031 Overall population: 0.0034	

Supportive study(ies)

The long-term efficacy of efgartigimod PH20 SC was evaluated in the ongoing, open-label study ARGX-113-1902, which is an extension of ARGX-113-1802.

Participants

Participants in the OLE phase included those who have continued treatment since Stage B of ARGX-113-1802 and those who have reinitiated efgartigimod PH20 SC treatment after receiving placebo in Stage B. Patients who were in the run-in period, Stage A or Stage B of ARGX-113-1802 at the time of the target number of events for the primary endpoint analysis (the 88th event in Stage B) could also roll-over to the OLE. Results for ARGX-113-1902 are presented for the overall population only.

Treatment

Treatment with efgartigimod PH20 SC 1000 mg in the abdominal skin area once weekly, for up to 2 years after marketing authorization in the participant's local country or until efgartigimod PH20 SC becomes commercially available for patients with CIDP or becomes available via a continued access program, whichever comes first. In a substudy, participants whose clinical condition was stable with weekly dosing for ≥12 weeks, could receive efgartigimod PH20 SC 1000 mg at 2 lower dosing frequencies (once every 2 weeks or once every 3 weeks) (n=5). Patients experiencing clinically relevant deterioration (defined by confirmed adjusted INCAT score increase of ≥1 point compared to study day 1 of the OLE) will be given the option to either continue with weekly efgartigimod PH20 SC or to be withdrawn from the trial. Patients will be treated as considered appropriate by the investigator, after they are withdrawn from the trial.

Primary and secondary objectives of ARGX-113-1902

The primary objective is to assess the long-term safety and tolerability of efgartigimod PH20 SC in CIDP.

Secondary objectives:

- To determine the long-term treatment effect.
- To evaluate the immunogenicity (anti-drug antibodies [ADA]) of efgartigimod and rHuPH20.
- To evaluate the PK of efgartigimod PH20 SC.
- To evaluate the PD effect of efgartigimod PH20 SC (ie, IgG levels).
- To evaluate additional patient-reported outcomes (including patient-reported quality of life and satisfaction with treatment).
- To explore self-administration of the treatment.

Primary endpoints of ARGX-113-1902

- Incidence of AEs and serious AE (SAEs) by System Organ Class (SOC) and preferred term (PT)
- Incidence of clinically significant laboratory abnormalities

Secondary endpoints of ARGX-113-1902

- Change from baseline (final visit in ARGX-113-1802 was used as baseline) over time in: aINCAT score; MRC sum score; 24-item I-RODS score; TUG score; Mean grip strength assessed by Martin-Vigorimeter
- Percentage of participants without clinical deterioration over time (clinical deterioration was defined as an increase in ≥1 point in aINCAT score compared to baseline).
- Change from baseline (final visit in ARGX-113-1802 was used as baseline) over time in EQ-5D-5L, BPI-SF, TSQM-9, RT-FSS, and HADS
- Changes from baseline (final visit in ARGX-113-1802 was used as baseline) over time of serum IgG levels (total).

Results

In total, 226 of 228 (99.1%) eligible participants in ARGX-113-1802 rolled over to the ARGX-113-1902. Additionally, 3 ineligible participants (without clinical deterioration in Stage B) enrolled in ARGX-113-1902, resulting in a total of 229 participants who entered ARGX-113-1902. Out of these 229 participants, 228 had received at least 1 administration of efgartigimod PH20 SC in ARGX-113-1902. A high

percentage of participants (196 [86.0%]) were ongoing in the study as of the clinical data cutoff date (15 Jun 2023). Three (1.3%) participants completed the study, and 29 (12.7%) participants were withdrawn from the study, this was mainly due to AEs (3.1%, n = 7), withdrawal by subject (3.5%, n = 8) and lack of efficacy (2.6%, n = 6). At the time of this interim analysis, 100 participants have been in ARGX-113-1902 for 24 weeks or longer, 58 for 48 weeks or longer, and 12 for 96 weeks or longer.

Patient characteristics

In the total group, the mean (SD) study duration was 31.86 (30.226) weeks. However, participants in the 1802 Stage B PBO group have had a longer study duration than those in the 1802 Stage B EFG PH20 SC group, with mean (SD) treatment durations of 39.69 (33.769) and 30.80 (27.193) weeks, respectively, because these participants withdrew from ARGX-113-1802 earlier than participants in the 1802 Stage B EFG PH20 SC group.

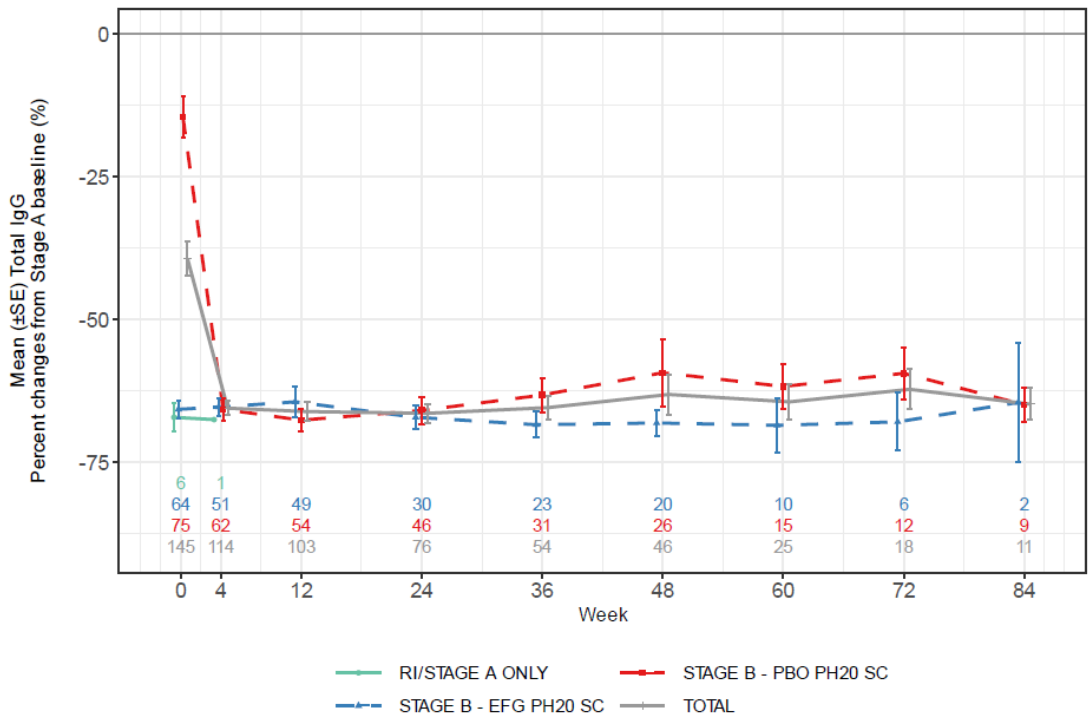
The median (min, max) age for participants was 56.0 (21, 83) years. There was a higher percentage of males (62.3%) compared to females (37.7%), and most participants were White (62.2%); approximately a third were Asian (29.8%). As of the OLE baseline visit, the median (min, max) time since CIDP diagnosis in the total group was 3.25 (0.3, 46.3) years.

Approximately half (45.6%) of the participants had received IVIg or SCIg as the most recent prior CIDP therapy before ARGX-113-1802, 51 (22.4%) had received corticosteroids as the most recent prior CIDP therapy, and 73 (32.0%) were treatment-naïve. At Stage A baseline in ARGX-113-1802, the mean (SD) total INCAT score, I-RODS score, and mean grip strength of the dominant hand were 4.5 (1.62), 41.2 (15.38), and 39.0 (23.60) kPa, respectively.

Pharmacodynamics

Efgartigimod PH20 SC reduced total IgG levels consistent with its mechanism of action. The percentual change from Stage A baseline over time in total IgG is presented in Figure 36.

Figure 36: Percent change from stage A baseline over time in total IgG (safety analysis set)

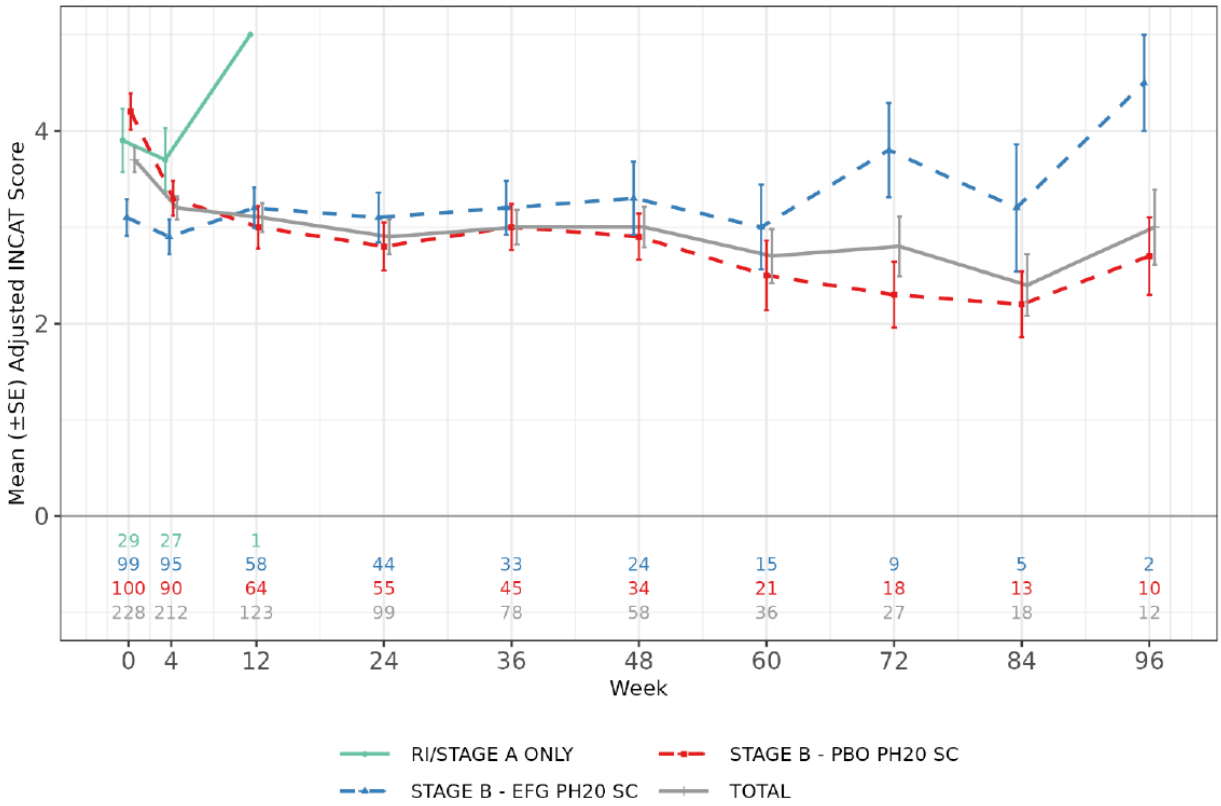


EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IgG=immunoglobulin gamma; PBO=placebo; RI=run-in during ARGX-113-1802; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Long-term efficacy results from OLE phase (ARGX-113-1902)

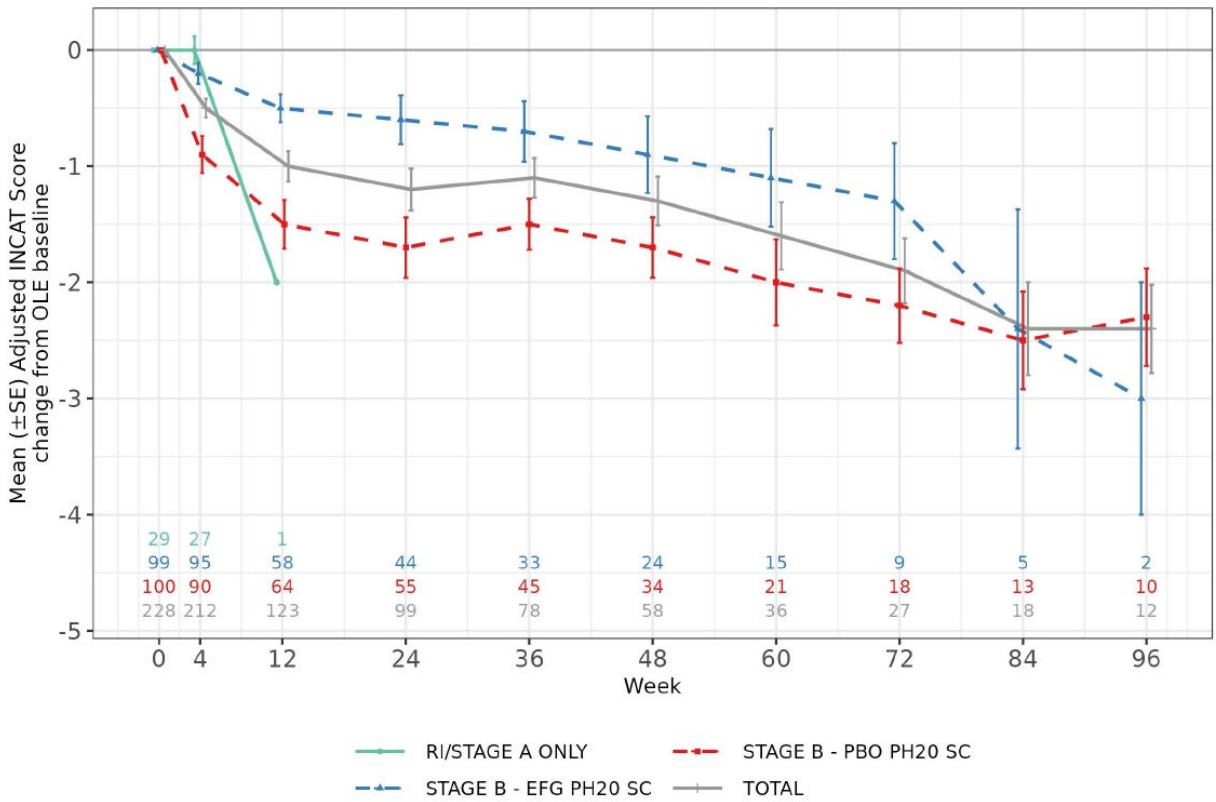
aINCAT score

Figure 37: Study ARGX-113-1902: aINCAT Score: Mean Actual Values Over Time (mITT Analysis Set)



EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; INCAT=Inflammatory Neuropathy Cause and Treatment; mITT=modified intent-to-treat; PBO PH20 SC=placebo; RI=run-in during ARGX-113-1802; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured.

Figure 38: Study ARGX-113-1902: aINCAT Score: Mean Changes From OLE Baseline Over Time (mITT Analysis Set)

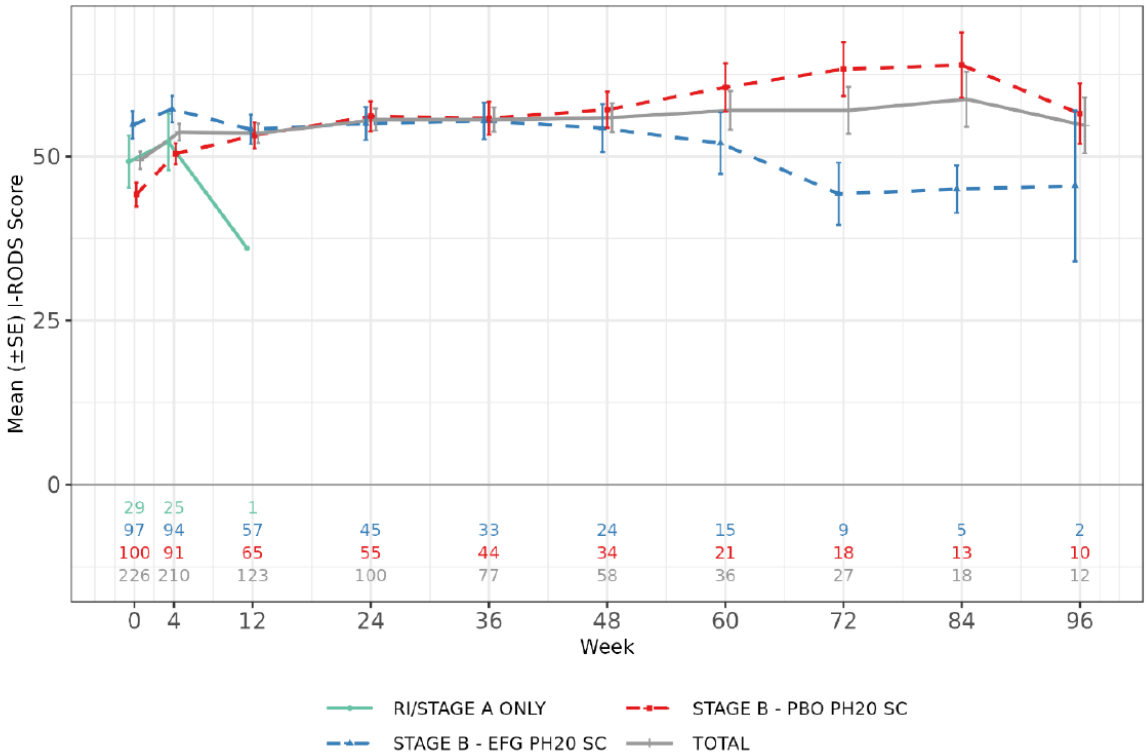


EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; INCAT=Inflammatory Neuropathy Cause and Treatment; mITT=modified intent-to-treat; OLE=open-label extension; PBO PH20 SC=placebo; rHuPH20=recombinant human hyaluronidase PH20; RI=run-in during ARGX-113-1802; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured

Both Stage B groups had decreased aINCAT scores from the OLE baseline. The Stage B placebo group had the greatest decrease in aINCAT scores through week 48; the mean (SE) decrease in aINCAT scores was evident as early as week 4 (−0.9 [0.16]), the earliest time point at which efficacy assessments were measured, indicating improvement. Further improvement in the Stage B placebo group was observed by week 12 (−1.5 [0.21]), after which scores plateaued and were stable through week 48 (−1.7 [0.26]).

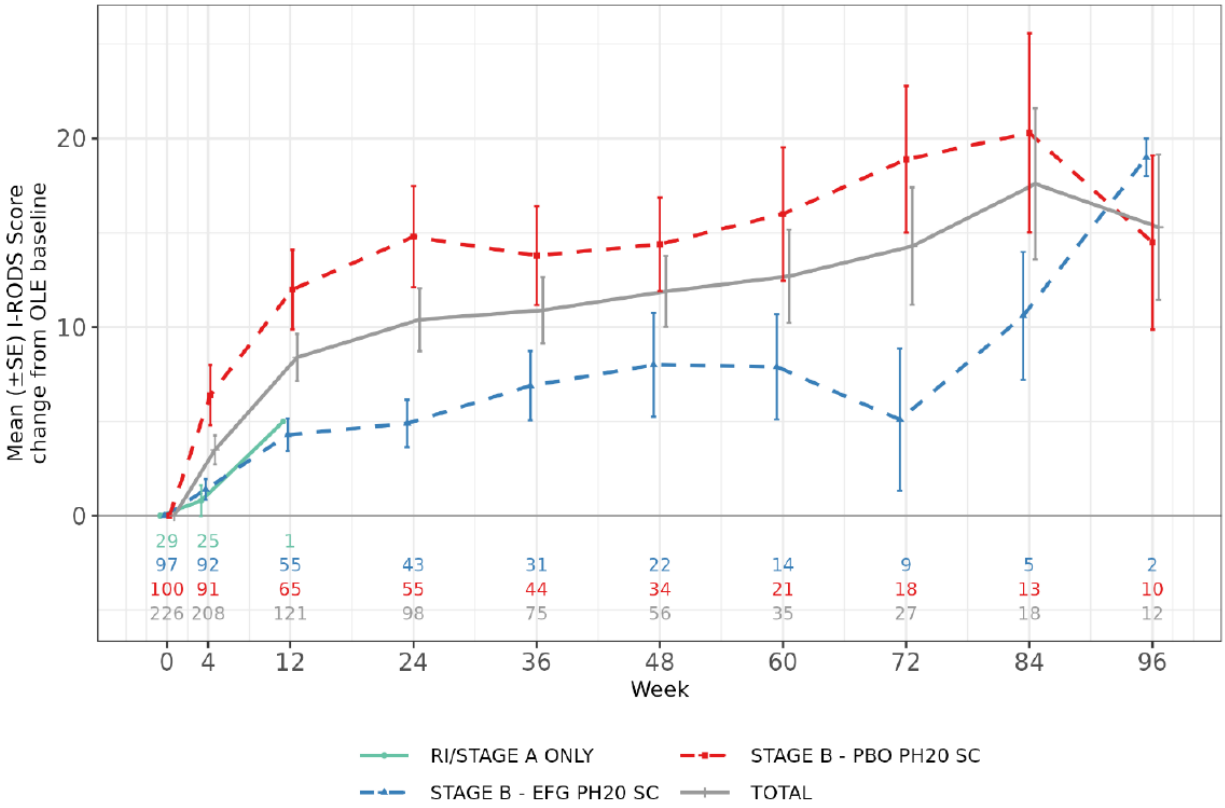
I-RODS score

Figure 39: Study ARGX-113-1902: I-RODS Score: Mean Actual Values Over Time (mITT Analysis Set)



EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; I-RODS=Inflammatory- Rasch-built Overall Disability Scale; mITT=modified intent-to-treat; PBO PH20 SC=placebo; rHuPH20=recombinant human hyaluronidase PH20; RI=run-in during ARGX-113-1802; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured

Figure 40: Study ARGX-113-1902: I-RODS Score: Mean Changes From OLE Baseline Over Time (mITT Analysis Set)

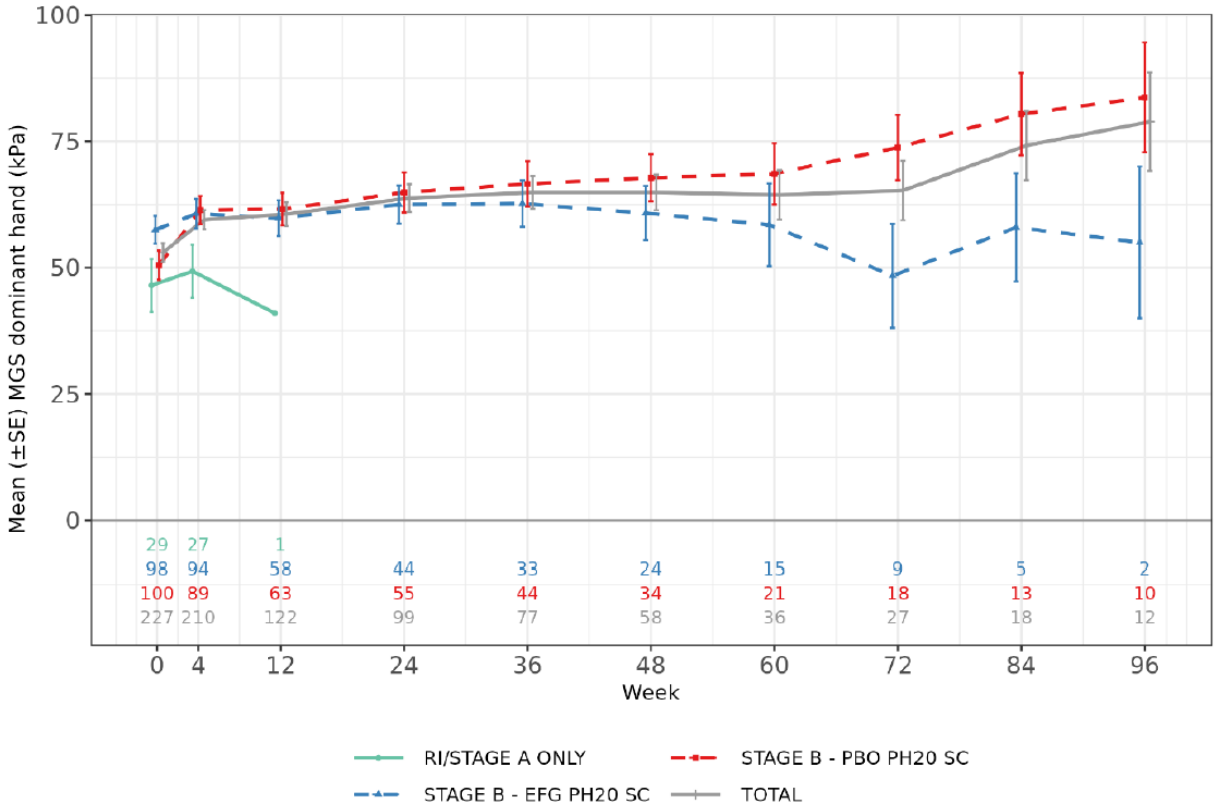


EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; I-RODS=Inflammatory- Rasch-built Overall Disability Scale; mITT=modified intent-to-treat; OLE=open-label extension; PBO PH20 SC=placebo; rHuPH20=recombinant human hyaluronidase PH20; RI=run-in during ARGX-113-1802; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured

Both Stage B groups had increases in I-RODS score from OLE baseline over time with efgartigimod PH20 SC treatment. The Stage B placebo group had the greatest increases in I-RODS scores, indicative of improvement; mean (SE) increases in this group were evident as early as week 4 (6.4 [1.60]), the earliest time point at which efficacy assessments were measured, with further improvements evident by week 12 (12.0 [2.11]). After week 12, mean (SE) scores were stable through week 48 (14.4 [2.48]).

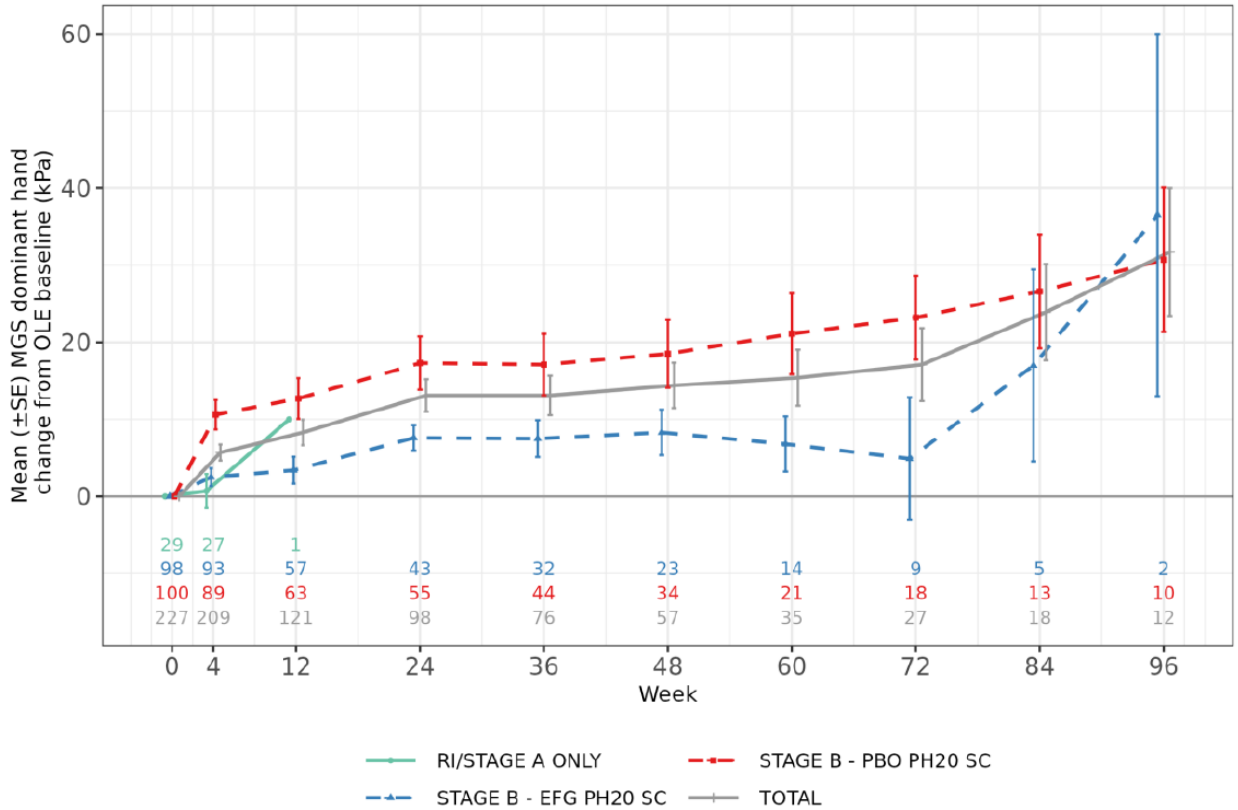
Mean grip strength (dominant hand)

Figure 41: Study ARGX-113-1902: Mean Grip Strength: Mean Actual Values Over Time in Dominant Hand (mITT Analysis Set)



EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; MGS=mean grip strength; mITT=modified intent-to-treat; PBO PH20 SC=placebo; rHuPH20=recombinant human hyaluronidase PH20; RI=run-in during ARGX-113-1802; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured.

Figure 42: Study ARGX-113-1902: Mean Grip Strength: Mean Changes From OLE Baseline Over Time in Dominant Hand (mITT Analysis Set)



EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; MGS=mean grip strength; mITT=modified intent-to-treat; OLE=open-label extension; PBO PH20 SC=placebo; rHuPH20=recombinant human hyaluronidase PH20; RI=run-in during ARGX-113-1802; SC=subcutaneous(ly)
Notes: ARGX-113-1902 baseline corresponds to the last available value before the first EFG PH20 SC administration in ARGX-113-1902. Week 4 was the first time point at which efficacy assessments were measured.

Both Stage B groups had increases in mean grip strength from the OLE baseline. The greatest improvements were observed in the Stage B placebo group, with mean (SE) increases observed by week 4 (10.6 [1.91] kPa, dominant hand), the earliest time point at which efficacy assessments were measured, and remaining stable through week 48 (18.5 [4.40] kPa for the dominant hand).

MRC Sum Score

In the total group, the mean (SE) change from the OLE baseline for the MRC sum score was 2.8 (0.46) at week 12 and 3.7 (0.74) at week 48.

TUG Test Score

In the total group, the mean (SE) change from the OLE baseline for the TUG test score was −2.8 (0.53) seconds at week 12 and −2.2 (0.78) seconds at week 48.

Patient-Reported Outcomes and Quality-of-Life Measurements

Mean (SE) change in EQ-5D-5L visual analogue scale scores (total group) showed a trend of improvement from baseline at week 12 (11.0 [1.95]) and week 48 (14.5 [2.88]).

Clinical deterioration

Of the 55 patients followed up to week 48 in the OLE phase n = 5 (9.1%) had clinical deterioration during the OLE phase.

Historical placebo effect in CIDP

The percentage of participants with confirmed ECI during Stage A was consistent with that reported for historical studies of IVIg and SCIg. In addition, the data from Stage B align with the reported efficacy of immunoglobulins in relapse prevention. An overview of the design and efficacy results of the main historical immunoglobulin studies conducted in CIDP is provided in comparison with ARGX-113-1802 in Table 40.

Table 40: Overview of design and efficacy of the main historical immunoglobulin studies conducted in CIDP vs. Study ARG-113-1802

	ICE[59]	**PRIMA**[61,83]	**PATH**[58,83]	**ProCID**[60,62]	**ARGX-113-1802**
IMP	IVIg	IVIg	IVIg and SCIg	IVIg	Efgartigimod PH20 SC
Treatment-free washout period (run-in)	No	Yes	Yes	Yes	Yes
Duration (induction period)	24 weeks (placebo controlled)	24 weeks (open label)	12 weeks (open label)	24 weeks (open label)	12 weeks (open label)
Number of patients by prior treatment status	Total: 117 IVIg: 32 (27%) Treatment-naïve: 85 (73%)	Total: 28 IVIg: 13 (46%) Treatment-naïve: 15 (54%)	Total: 207 All IVIg	Total: 69 IVIg: 9 (13%) CS: 60 (87%)	Total: 322 IVIg or SCIg: 165 (51%) CS: 63 (20%) Treatment-naïve: 94 (29%)
Definition of response	Improved ≥1 point in aINCAT score by week 6 and maintained improvement vs baseline until week 24; no worsening at any time until week 24 vs baseline	Improved ≥1 point in aINCAT score by week 24 or at early discontinuation	Improvement in aINCAT score to at least screening level and maintained for last 3 weeks of week 12 period	Improved ≥1 point in aINCAT score by week 6 and maintained improvement vs baseline until week 24; no worsening between weeks 3 and 21; no discontinuation	Confirmed ECI (on 2 consecutive visits) between weeks 4 and 12
Response percentage by pretreatment					
Total	IVIg: 28/59 (48%)[a] PBO: 13/58 (22%)	17/28 (61%)	151/207 (73%)	55/69 (80%)	214/322 (66%)
IVIg	IVIg: 11/20 (55%) PBO: 0/12 (NC)	10/13 (77%)	151/207 (73%)	5/9 (56%)	97/165 (59%)[b]
Treatment-naïve	IVIg: 17/39 (44%) PBO: 13/46 (28%)	7/15 (47%)	NA	NA	68/94 (72%)
CS	NA	NA	NA	50/60 (83%)	49/63 (78%)

Sources: Hughes et al[59]; Léger et al[61]; Merkies et al[83]; van Schaik et al[58]; Cornblath et al[60]; Cornblath et al[62]
CS=corticosteroids; ECI=evidence of clinical improvement; aINCAT=adjusted Inflammatory Neuropathy Cause and Treatment; IVIg=intravenous immunoglobulin; NA=not assessed; NR=not reported; PBO=placebo
[a] The reported response percentage in the label (Gamunex-C US prescribing information[43]) is 48% (28/59), and the published percentage is 54% (32/59).
[b] These data are for prior CIDP therapy in the IVIg or SCIg subgroup.

ICE was a placebo-controlled study investigating the efficacy of IVIg for induction and maintenance therapy in patients with CIDP untreated for at least 3 months. The PATH study tested the ability of IVIg to restabilize patients with CIDP after IVIg withdrawal and disease worsening, followed by a placebo-controlled maintenance phase with SCIg. The PRIMA study also tested the efficacy of IVIg as induction treatment. The ProCID study investigated the efficacy of IVIg in pretreated patients, the majority with corticosteroids, as induction treatment in CIDP.

Given the difference in response definition, study design, and population, comparison of response rates is not straightforward; however, the response rate in Stage A of ARGX-113-1802 (66.5%) aligns with other open-label CIDP studies and was higher than the response rate in the only placebo-controlled study in both the active treatment (48%) and placebo (22%) arms (ICE study). A meta-analysis of response rates in the placebo groups from previous CIDP studies demonstrated that in studies with a primary endpoint of improvement, the mean response in the placebo groups was 11.2% (95%CI: 4.1%-20.5%). Acknowledging the differences between studies, the response rate of 66.5% (95% CI: 61.0%-71.6%; Section 4.1.3) with efgartigimod PH20 SC exceeds the response with placebo; the lower bound of the CI for the efgartigimod PH20 SC response is substantially higher than the upper bound of the CI for placebo, indicating a treatment effect superseding a potential effect created by chance.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The subject of this application is efgartigimod for SC administration in patients with CIDP with active disease. Efgartigimod is a human IgG1 antibody Fc fragment and a natural FcRn ligand. By blocking FcRn, efgartigimod reduces the levels of circulating disease-causing IgG antibodies. CIDP is a rare, autoimmune disease of the peripheral nervous system. Peripheral nerve demyelination causes progressive or remitting muscle weakness and sensory disturbances. Presence of some axonal loss, and resulting permanent neurological deficits, is common. Treatment efforts are directed at the immune mediated destruction of the myelin sheaths and include IVIg, SCIg and PLEX as well as broader immunosuppressive agents e.g. corticosteroids. An unmet need exists as many CIDP patients have debilitating symptoms, even with treatment, and due to the potential AEs linked with current therapies. In recent years global supply chain shortages of IVIg/SCIg, which is dependent on plasma donors, has occurred.

Study design

The clinical efficacy of efgartigimod in CIDP is supported by a single, pivotal phase 2 study (ARGX-113-1802) investigating efficacy, safety, tolerability, immunogenicity, PK and PD in adults with probable or definite CIDP as established by independent experts. Supportive evidence includes an ongoing, open-label study (ARGX-113-1902), an extension of ARGX-113-1802, data from published CIDP trials, including the historical placebo effect in this population, and a mechanistic rationale related to the IgG lowering mechanism of action of efgartigimod.

ARGX-113-1802 used a randomized withdrawal design conducted in 2 stages (A and B). Prior to Stage A patients were withdrawn from current CIDP treatments and recent evidence of clinical meaningful deterioration was required in order to exclude patients without active CIDP (decrease of aINCAT/I-RODS/grip strength). Stage A was open-label with all participants receiving efgartigimod for 4-12 weeks. The primary endpoint of Stage A was the percentage of participants with confirmed ECI as measured by pre-defined clinical scores (aINCAT and in specific cases I-RODS or grip strength). Stage A responders with confirmed ECI entered Stage B. Stage B was a randomized, double-blind withdrawal study in which participants were monitored for relapse (worsening of ≥1 point on the aINCAT score) after being randomized to either placebo or continued efgartigimod for up to 48 weeks. Stage B was stopped at the time of the 88th relapse and the primary endpoint was time to first relapse compared to Stage B baseline. In Stage A and Stage B efgartigimod was used as monotherapy for CIDP.

Concerns related to the study design

It is acknowledged that, given the context of a randomized withdrawal design, ARGX-113-1802 is well designed and executed. CIDP is a difficult condition in which to conduct randomized placebo-controlled trials, given the low disease prevalence (prevalence of 0.8-8.9:100.000), the issue of frequent misdiagnosis, and the need to ascertain disease activity before inclusion (i.e. with a run-in period in which the patients clinical condition worsens as a sign of ongoing immunological activity). In such circumstances a single pivotal trial showing short-term efficacy (proof-of-concept) may be acceptable as evidence to support a marketing authorization for a new indication, **if** the study is controlled and the data compelling (*Points to consider on application with 1. Meta-analyses, 2. One pivotal study, CPMP/EWP/2330/99, EMA*). Considered in isolation, the endpoints and the inclusion/exclusion criteria of ARGX-113-1802, are acceptable, however, major concerns about the ability of ARGX-113-1802 to provide sufficient evidence of short-term efficacy of efgartigimod in CIDP were raised due to major methodological limitations of the study design.

Given the open label design and lack of control group, it was questioned whether Stage A provided sufficient internal validity to establish efficacy of efgartigimod in CIDP. Further, only patients who responded to and tolerated efgartigimod in Stage A were selected to enter the randomized controlled phase, Stage B, therefore significant bias was introduced in the direction of overestimating efficacy. Indeed, it appears likely that drug response in Stage A was correlated to the primary endpoint in Stage B (relapse after drug withdrawal vs. drug continuation). This introduced bias favouring efgartigimod and the efficacy of efgartigimod in CIDP may be overestimated. Further bias, favouring efgartigimod, may be introduced by a rebound effect e.g. drastic clinical worsening after sudden cessation of CIDP treatment prior to Stage A. It was considered plausible that the clinical deterioration seen with abrupt discontinuation of previous therapy may spontaneously stabilize in the post-withdrawal weeks. As clinical deterioration, after withdrawal of therapy, lead directly into an open label phase (Stage A), where short-term improvement (2 consecutive visits one week apart) constituted the patient as an efgartigimod responder, a rebound effect with some, spontaneous stabilization in Stage A, may overestimate the efficacy of efgartigimod.

As part of the responses, the Applicant has argued that the ethical and feasibility concerns are sufficiently significant so as to preclude a large-scale clinical trial investigating placebo versus IMP ***and*** including run-in. The Applicant discusses several circumstances in favour of considering exceptional circumstances, which would potentially allow the use of historical control data (*Guideline on clinical trials in small populations, London 2006, CHMP/EWP/83561/2005*).

CIDP is rare (estimated prevalence of 0.8-8.9 per 100.000 person years), difficult to diagnose, disabling and it can be a primary and secondary cause of fatality. Peripheral nerve demyelination causes proximal weakness (i.e. difficulties rising from seated position, stair climbing), distal weakness (i.e. "foot drop", impaired fine motor skills in daily activities), sensory disturbances and neuropathic pain. In a clinical questionnaire 75.6% reported disability in upper limbs, 26.8% reported need of unilateral walking

support, 14.6% bilateral support and 17.1% use of wheelchair (Mahdi-Rogers et al, 2014). Cranial nerve and bulbar affliction are present in about 11% of typical CIDP patients (Shibuya et al, 2020). A study published in 1975, following 53 patients with CIDP for an average of 7.5 years finds that 25% became confined to a wheelchair and 10% died from the disease (Dyck et al., 1975). Overall, with regards to morbidity and mortality, the cited studies are small and several biases exist. The Applicant has not provided extensive scientific documentation of the natural history of CIDP, but given the rarity and heterogeneity of the disease, and the multitude of diagnostic criteria proposed since the first description of CIDP, the documentation provided is considered sufficient. The CHMP agrees that CIDP can be severely disabling and associated with increased mortality.

In terms of feasibility, the Applicant argues against use of placebo directly after a run-in period. The clinical worsening in the run-in period is necessary to avoid inclusion of patients with inactive disease characterized by neurological deficits due to secondary axonal degeneration and lack of immunologically mediated symptoms. In the literature this distinction of patients with active disease is frequently discussed as a challenge in clinical trials and clinical practice (overtreatment). Patients with symptoms not mediated by immunological activity would not be expected to respond to immunomodulatory and/or suppressive treatment options such as IVIG, SCIG, efgartigimod, corticosteroids or PLEX. The inclusion of run-in periods to ensure disease activity is generally recommended in trials across the literature (i.e. Bunschoten et al., 2019). The Applicant argues that randomization to placebo after run-in (in which patients have clinical deterioration) is neither ethical nor feasible, and only one study combining run-in with subsequent randomization to placebo versus active has been located (van Doorn et al., 1990). This trial included only 7 patients and was a short-term cross-over design. This type of study is not comparable to a clinical trial for registrational purposes, but, the authors of van Doorn et al., 1990 specifically mention that patients were reluctant to discontinue treatment and deteriorate prior to trial entry.

It is acknowledged that a run-in phase to demonstrate active disease is best practice in CIDP clinical trials. The fact that the disease is rare complicates this selection process, as a significant number of patients with a CIDP diagnosis may not be eligible. Other means of ensuring disease activity, i.e. exclusively including patients with new-onset disease, is not feasible given the low incidence of CIDP (crude incidence rate of 0.73:100.000-person years in people over the age of 55).

Ethical issues of randomizing patients with active disease could potentially be ameliorated by strict adherence to a rescue protocol and by randomisation schemas other than 1:1. The Applicant raises concerns about secondary axonal damage, which is valid, but it is not documented by the Applicant that this is likely to occur within the timeframe between randomization and exit to a rescue strategy. In the PATH study restabilisation with IVIG after treatment cessation lasted for 13 weeks and in 11% even 13 weeks was not sufficient for restabilisation. Thus, even if patients could be rescued in time to avoid secondary axonal degeneration, they would likely have significant concerns about such a long period of disease worsening. Now, ARGX-113-1802 does in fact require active patients to be randomized to placebo. Thus, the potential for secondary axonal damage also exists in part B of the study. However, the Applicant claimed that these patients are responders to efgartigimod and thus, given worsening in Stage B after randomization to placebo the patient can quickly access efgartigimod as an effective rescue in the open-label extension. Furthermore, the setting of a SAT using externally controlled data reduces the number of consecutive weeks during which the patient needs to be off treatment. A PCB-controlled phase after run-in would likely have a duration of up to 12 weeks (similar to Stage A in 1802) in order to evaluate efficacy of EFG vs PCB. Patients randomized to PCB would not only be required to accept the risk of further worsening, in which case rescue could be used, but also be required to accept that the worsening in their disability, as produced by the run-in phase, is not treated for an extended period compared to the setting of a SAT using externally controlled data. While, a short PCB-Controlled trial with a run in period including measures to limit the exposure of active patients to PCB (e.g. randomisation schemas other than 1:1 and time to event design ensuring a quick access to rescue therapies) is also

considered a feasible option, the CHMP acknowledges that it is difficult to determine which approach is more feasible or ethical, as both approaches have drawbacks. Other clinical trial designs, i.e. a non-inferiority trial, may be limited by rarity of the disease, as a large sample size would typically be required. "Restabilisation" approaches, as used in PATH, on the other hand may be subject to concerns of carry-over effects..

The Applicant discussed the historical placebo effect of ~20% originating from the ICE trial (IVIg versus placebo). The gap between the placebo-effect observed in the ICE study and the response rate in Stage A of (ARGX-113-1802) is acknowledged. However, this was not considered sufficient supportive documentation to compensate for the lack of internal validity in Stage A. Important differences between the ICE study and ARGX-113-1802 were identified, and concerns were raised about consistency as the placebo response rate of only one study (ICE) was discussed. Most notably, the ICE study defined responders exclusively by ~ 4 months of uninterrupted improvement on the aINCAT score. This definition is stricter than the ARGX-113-1802 definition in terms of magnitude of response (aINCAT only) and duration of response. A shorter duration of response may inflate response rates of ARGX-113-1802 compared to ICE. The Applicant performed a *post hoc* analysis in participants from ARGX-113-1802, who were considered to better reflect the ICE population (n=36), as they had no run-in period and improvement was assessed based on aINCAT only. The response rate was similar to the overall response rate in Stage A (69.4%). However, this small sub-population of ARGX-113-1802 does not address the concerns on inflation of responder rate. In summary, there are many aspects that make the comparison between ARGX-113-1802 and ICE biased, and the size of this bias cannot be quantified. In further support of the claimed historical placebo response rate the Applicant provided an analysis of a publication from 2020 (Lewis et al, *"Placebo effect in chronic inflammatory demyelinating polyneuropathy: The PATH study and a systematic review"*, J Peripher Nerv Syst*).* In short, this review identified placebo-controlled CIDP trials, and conducted a meta-analysis of the placebo response rate across all studies with a primary endpoint of improvement. An overall placebo response rate of 11% (95% CI: 4;21) was determined. In total 9 studies, in which endpoints were defined by improvement, were presented (Lewis et al., 2020). One study was presented in the dossier – but not discussed in Lewis et al., 2020 or by the Applicant (Dyck et al., 1982) but is included in the response assessment. Important methodological differences in terms of primary endpoint, duration, sample size and population exist between these studies and ARGX-113-1802. Thus, the Applicant has not presented a placebo-controlled study, which is substantially more similar to ARGX-113-1802, than ICE. Concerns about the biases associated with comparison of studies with different methodologies still exist. Several of the submitted placebo-controlled studies – given their publication 20+ years ago – deals with significantly different endpoints and clinical diagnostic criteria, all of which may be outdated at the present time. Furthermore, several studies are small, lack details, use cross-over designs and are prone to biases (i.e. not counting or following dropouts). This said, most studies have a placebo response rate in the vicinity of 20%, although some are significantly smaller (3 studies ranging from 0-9.5%) and larger (1 study of 42% and one study – potentially – up to 35%). In summary, the provided studies – keeping the significant methodological differences in mind – are supportive of a placebo response rate of about 20% in CIDP. Hence, the provided supplementary data are considered sufficient to estimate a historical placebo response rate.

In addition, the Applicant provided a mechanistic rationale for the use of IgG lowering therapies in CIDP. It is considered likely that CIDP pathophysiology is closely linked to pathological IgGs, and that the effect of other well-established therapies (PLEX, IVIg/SCIg) is closely linked to their ability to decrease the level of circulating IgG, which is also the mechanism of action of efgartigimod. Evidence of a significant mechanistic rationale for use of efgartigimod in CIDP is acknowledged by the CHMP. Additionally, a longitudinal figure of mean aINCAT scores throughout ARGX-113-1802 and ARGX-113-1902 was presented (responders). This showed a clear and renewed treatment response in the OLE upon re-introduction of efgartigimod in responders withdrawn from efgartigimod in Stage B. Included sensitivity analyses of the Stage B efficacy results were robust.

In conclusion, limitations remain, especially with respect to internal validity of the single pivotal study and population enrichment in Stage B. However, the opinion of the CHMP is that the Applicant has been able to sufficiently justify several specific circumstances that collectively justify exceptional circumstances. This includes disease rarity and heterogeneity, feasibility and ethical concerns of designing large, clinical trials, and the fact that the disease is disabling and potentially fatal. Given this, use of historical placebo rates, in addition to the results of ARGX-113-1802, is considered acceptable by the CHMP. To supplement the evidence provided by the ICE study the Applicant submitted an analysis of older placebo-controlled trials in CIDP. None are substantially more similar to ARGX-113-1802 than the ICE study. Thus, concerns about the biases associated with comparison of studies with different methodologies still exist. It does, however, appear that most of the presented placebo-controlled studies have a placebo response rate in the vicinity of 20%. This increases the confidence that the placebo response rate in ICE is within the scope of the "true" placebo response rate in patients with CIDP.

Hence, given the mechanistic rationale, the large margin to the historical placebo effect in ICE and several other studies, the unmet need in a difficult to study population, and the robust results of sensitivity analyses, it is considered sufficiently documented that EFG is efficacious in CIDP.

Major concerns related to the proposed indication wording (section 4.1 of the SmPC)

The initially claimed indication was "… *CIDP with active disease despite treatment with corticosteroids or immunoglobulins".* This was not considered to be in line with the studied population.

First, the study design does not allow to investigate *an add-on* treatment (e.g. to corticosteroids). It is not possible to assess if patients in ARGX-113-1802 study actually experienced *added benefit* because the patients switched from a previous treatment to Vyvgart that was evaluated as a monotherapy strategy. The statement "*despite treatment with corticosteroids or immunoglobulins*" in the proposed indication in section 4.1 was unclear as it may be misinterpreted as recommendation to use the treatment as an *add-on* to corticosteroids or immunoglobulins. It should be clearly stated in the indication that efgartigimod should be used as monotherapy, as it was evaluated in the pivotal trial.

Second, the study design does not allow any head-to-head comparisons, e.g. to IVIg/SCIg or corticosteroids. Thus, the study design does not allow to conclude on whether Vyvgart is more efficacious than any other medicinal products for the condition. Further, the pre-treated participants were requested to withdraw the background therapy for CIPD to be considered eligible regardless of effectiveness of the background therapy to control the ongoing inflammatory activity of the condition. In order words, most participants enrolled in the trial were indeed priorly treated with corticosteroids or immunoglobulins. However, this does not equate to state that these participants were necessarily inadequately controlled by corticosteroids or immunoglobulins. Participants needed to have a certain degree of current disability (i.e. INCAT of at least 2 points) but this could have been occurred due to a prior inflammatory event leading to neurodegeneration. Therefore, the statement "*despite treatment with corticosteroids or immunoglobulins*" was not considered to be supported by the study design (regardless of whether results from the pre-treated or overall population are used). The wording could be misinterpreted as the enrolled population included mainly pre-treated participants with suboptimal control of the condition. Thus the Applicant was requested to change the wording of the indication

In response, the Applicant proposed the following, revised indication in 4.1.:

"*Vyvgart is indicated for the treatment of adult patients with CIDP with progressive or relapsing active disease after prior treatment with corticosteroids or immunoglobulins."*

The CHMP agreed on the statement *after prior treatment with corticosteroids or immunoglobulins* to reflect that the vast majority of the studied population was previously exposed to either corticosteroids or immunoglobulins (only ~10% of patients in Stage A were treatment-naïve). This should be however not misinterpreted as if Vyvgart was evaluated in patients for whom corticosteroids and immunoglobulins were used and discontinued due to treatment failure as explained above.

The CHMP requested again the Applicant to reflect that the treatment is *monotherapy* (all patients were discontinued from their CIDP treatment. In addition, the CHMP requested the terms "*progressive or relapsing"* to be deleted and "*active*" to be added before "CIDP".

The Applicant agreed to insert monotherapy, but argued to keep progressive or relapsing as this would align with the description of the condition in guidelines. The proposed indication thus reads:

Vyvgart is indicated as monotherapy for the treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins.

This suggestion, and the argument relating to guidelines, is accepted.

A major objection was raised as patients with pure sensory CIDP were excluded from the pivotal study – but not in the indication. However, the Applicant justified the inclusion of sensory CIDP in 4.1 sufficiently, arguing that sensory CIDP is a variant of typical CIDP which can be assessed with the same clinical scores as typical CIDP and can be treated with IVIg/SCIg and PLEX. Considering this, and the rarity of sensory CIDP, it is accepted that the indication statement does not exclude sensory CIDP.

Concerns related to external validity

Initially, concerns were also raised on the external validity of the study design. It was questioned whether the study participants were representative of the general population of patients with CIDP, as the study design Stage B primarily answered the question of whether responders to efgartigimod remained responders (i.e. patients with active CIDP, who improve after treatment with efgartigimod, are more likely to deteriorate if efgartigimod is withdrawn than if it is continued). In terms of generalizability and external validity the Applicant agreed to include a statement in the SmPC, which suggests clinical evaluation of the patient after 3-6 months of treatment with efgartigimod. It was proposed, by the CHMP, that this should include specific criteria from the clinical trial to assess the effect of efgartigimod. However, the Applicant argued that the design of the study (with a run-in period in which disease worsening was required) and the heterogeneity of CIDP patients did not allow the use of these in clinical practice. The Applicants proposal was endorsed, but it was suggested that a phrase is added on the continued monitoring of efficacy, which that Applicant accepted.

Efficacy data and additional analyses

Participants

In total 322 entered Stage A, of these, 101 participants were withdrawn; n = 36 due to lack of efficacy, n = 22 due to roll-over to OLE and n = 43 due to other reasons (including n = 20 due to AEs and n = 11 due to participant withdrawal, n = 5 due to "other"). In Stage B 221 participants (the responders; 68.6%) were randomized 1:1 to placebo or efgartigimod. At time of the 88th event in Stage B n = 64 (57.7%) in the efgartigimod arm had either completed 48 weeks in Stage B or had an event in Stage B, in the placebo group this number was n = 74 (67.3%).

For the most part, in Stage A and B the overall and pretreated populations were similar with respect to demography and disease characteristics, apart from pre-specified differences (CDAS score). The same applies for the active versus the placebo arm in Stage B. However, some significant differences were identified. In Stage B, time since CIDP diagnosis was shorter than in Stage A (median 2.2 years [0, 29]

versus 2.8 [0, 46] respectively in the overall population) and prior (within 6 months before screening) treatment with IVIg and SCIg was less frequent than in Stage A (43.4% in Stage B versus 51.2% in Stage A). In Stage B, pretreated population, median time from diagnosis was lower than in any other group (1.1 [0, 22] in active arm versus 2.0 [0, 15] in placebo arm), which is likely related to the definition of this group (high CDAS score).

A sub-group of participants were termed "treatment-naïve" and CHMP requested clarification in relation to this terminology. Patients in the treatment-naïve subset could, apparently, be previously treated for CIDP if this occurred > 6 months prior to screening. This was questioned, and the Applicant agreed that the terminology was imprecise, but opted to keep it in the AR as the term did not figure in the SmPC. This was agreed. The Applicant also presented evidence of the total number of actual, treatment-naïve patients at Stage A (i.e. patients with CIDP who never, at any time, received prior treatment). However, discrepancies were noted in the number of patients between the submitted response from the Applicant (N=31 with no prior treatment) and the CSR (N=21 with no prior treatment). This discrepancy was clarified by the Applicant, as the definition used in the CSR and reply are slightly different. In the reply patients were considered treatment-naïve if no disease-modifying therapies had been used previously, however, symptomatic treatment (i.e. pregabalin for neuropathic pain) was allowed. In the CSR neither symptomatic nor disease-modifying treatment was allowed. Defining treatment naïve-patients by use of disease-modifying therapy is endorsed by the CHMP, and thus ~10% of patients in Stage A were treatment-naïve. Of these, ~84% were treatment responders in Stage A. In Stage B relapse rates were 17.6% (n=3) in placebo versus 36.4%(n=4) in the active arm, this difference was not statistically significant which may be due to lack of power in this small sub-group.

Stage A

The proportion of ECI responders in the open label Stage A phase was 66.5-67.6%, and was similar in both the overall and the pre-treated populations. In Stage A, a significant number of patients discontinued the study (25.9-27% depending on population), especially patients previously treated with IVIg/SCIg had a high frequency of discontinuation (30-40%). This skewed withdrawal rate is considered problematic for the external validity of the study, especially given that the sought indication (section 4.1 of the SmPC) is based on a responder-only population, of whom a large part was recently treated with immunoglobulins as per definition of the eligibility criteria. The Applicant was asked to further describe discontinuations in all included groups and discuss, if necessary with supplementary *post hoc* sensitivity analyses, the expected impact on external validity**.** Furthermore, it was considered somewhat counter-intuitive that efgartigimod was less efficacious in patients previously responding to IVIg due to the PD overlap (prevention of recirculation of pathological immunoglobulins via the neonatal FcRn receptor). The Applicant was asked to discuss this paradox in the context of the efficacy data provided in Stage A and Stage B**.** The Applicant presented data on discontinuations as requested. In these data it was evident that especially patients recently treated with IVIg/SCIg group had a higher frequency of discontinuations in Stage A, and that these seemed to be mainly related to lack of efficacy/worsening of CIDP during Stage A. The Applicant documented that n=42/69 discontinuations in this group occurred before efficacy of efgartigimod could reasonable be assessed in Stage A (week 4). This was considered to be due to intolerance to the long treatment-free interval posed by the run-in period. Previous IVIg/SCIg are considered particularly treatment dependent as a group and thus more vulnerable to this. This explanation is considered to be likely from a clinical point of view. The long duration of the treatment-free run-in is not considered directly applicable to clinical praxis, but is a consequence of study design considerations.

Stage B

Participants in Stage B treated with efgartigimod had a reduced risk of relapse compared to placebo. Relapse occurred in 31 patients (27.9%) in the efgartigimod group versus n=59 (53.6%) in the placebo group with a HR of 0.394 (95% CI 0.253-0.614). In the pretreated population relapse was more frequent in the placebo group compared to the efgartigimod group (n=32, 68.1% versus n=13, 27.1, respectively). This corresponds to a HR of 0.269 (95% CI 0.138-0.523).

An increased propensity towards relapse in the placebo group of the pretreated population is also reflected in a shorter median time to clinical deterioration in the pretreated population versus the overall population (placebo group only: 140.0 [95% CI75.0 to NC] days in overall versus 56.0 [95% CI 34.0-140.0] days in pretreated). The relapse rate in the two active groups (overall versus pretreated) are similar. The primary endpoint in Stage B is thus met with high statistical significance. This finding is robust in extreme-case analysis and mixed-case analysis in the overall population.

The pretreated population is considered to be a more homogenous subset of the overall population (e.g. short disease duration and all are on treatment prior to Stage A). A lower number of patients in the Stage B pretreated population were treated with IVIg/SCIg (possibly conferred by geographic differences with a lower percentage from North America and European countries, in which immunoglobulin availability may be higher). Being recently diagnosed may increase the risk of relapse upon treatment withdrawal. Having long-term stable disease, and potentially being treatment refractory, would likely confer a less volatile disease state, in which progressions upon withdrawal of therapy may be less likely or drastic. Thus, the pretreated group is a group with several characteristics that make them potentially more likely to both respond to a treatment and relapse once treatment is withdrawn.

2.4.4. Conclusions on the clinical efficacy

In conclusion, limitations remain, especially with respect to internal validity of the single pivotal study and population enrichment in Stage B. However, the Applicant has been able to sufficiently discuss several specific circumstances that justify exceptional circumstances. Given this, use of historical placebo rates is acceptable. Concerns about the biases associated with comparison of historical placebo response rates exist as studies vary greatly in terms of methodology. Nevertheless, a placebo response rate in the vicinity of 20% is seen in the majority of studies, thus increasing the confidence that a 20% placebo response rate is within the scope of the "true" placebo response rate in CIDP. Given the strong mechanistic rationale, the large margin to the historical placebo effect in ICE and several other studies, the unmet need in a difficult to study population, and the robust results of sensitivity analyses, it is considered sufficiently documented that EFG is efficacious in CIDP.

Therefore, the benefit-risk of EFG for the treatment of CIDP is positive.

2.5. Clinical safety

Introduction

The subject of this application is efgartigimod for SC administration coformulated with rHuPH20 in patients with CIDP with active disease.

Efgartigimod alfa (ARGX-113) is a human IgG1 antibody Fc fragment, which is a natural FcRn ligand. Efgartigimod outcompetes endogenous IgG binding, preventing FcRn-mediated IgG recycling and increasing IgG degradation. Efgartigimod is being evaluated for severe autoimmune diseases mediated by pathogenic IgG autoantibodies, including CIDP. By blocking FcRn, efgartigimod reduces the levels of circulating disease-causing IgG antibodies.

Vyvgart (efgartigimod alfa IV) has received regulatory approval for patients with gMG in various jurisdictions, including the European Union, Japan, and the United States. Additionally, efgartigimod PH20 SC has received regulatory approval for patients with gMG in the United States, the European Union, and Japan. Relevant efgartigimod IV and PH20 SC data supporting this CIDP application are cross-referenced to the previously approved or submitted regional applications for gMG IV and gMG PH20 SC, respectively.

Patient exposure

As of 16 Dec 2023, the estimated cumulative number of participants exposed to efgartigimod in argenx-sponsored clinical studies is 1787, including 387 healthy participants and 1400 participants with IgG-mediated autoimmune diseases, including CIDP, gMG, primary immune thrombocytopenia, pemphigus, and bullous pemphigoid. Of these participants, approximately 1243 received efgartigimod PH20 SC.

The safety data of efgartigimod PH20 SC supporting this application for the treatment of adult patients with CIDP is primarily based on data from studies investigating efgartigimod as a single agent in participants with CIDP. The safety profile is further substantiated with safety data from studies investigating efgartigimod PH20 SC in healthy participants and participants with gMG, which were previously submitted as part of the gMG application.

The focus of this report is the safety evaluation from the following clinical studies in participants with CIDP:

- Completed pivotal study ARGX-113-1802 conducted in the following populations:
    - Overall population: all enrolled participants; analyses from the overall population form the basis of this submission and demonstrate the safety of efgartigimod PH20 SC in participants with CIDP.
    - Pretreated population: A subgroup of the overall population comprising participants who received CIDP therapy within 6 months before screening and had a CDAS score of ≥4 at screening. The results from the prespecified analyses in the pretreated population support the indication in the EU for the treatment of adult patients with CIDP with active disease despite treatment with corticosteroids or immunoglobulins.

This study was conducted in 2 stages: an open-label Stage A and a randomized-withdrawal, double-blinded, placebo-controlled Stage B with safety analyses conducted in the overall and pretreated populations.

- Ongoing study ARGX-113-1902, which is an open-label extension to antecedent study ARGX-113-1802. An IA of ARGX-113-1902 is presented. The IA includes all participants who had received treatment with efgartigimod PH20 SC as of the clinical data cutoff date of 15 Jun 2023. No analysis of participants in the pretreated population of ARGX-113-1802 was performed in ARGX-113-1902.
- A pooled analysis (pooling block, PB) that includes all participants with CIDP who received efgartigimod PH20 SC in ARGX-113-1802 and/or ARGX-113-1902. A pooled analysis including the pretreated population of ARGX-113-1802 was not performed.

Pooled Analyses of Data from Studies in Participants With CIDP

A CIDP PB was defined in support of the application for efgartigimod PH20 SC for the treatment of CIDP. All participants with CIDP who received at least 1 complete or partial dose of efgartigimod PH20 SC in ARGX-113-1802 and/or ARGX-113-1902 were included in the SAF of the PB.

The pooled analysis was performed to maximize the amount of efgartigimod PH20 SC safety data from participants with CIDP. It also allows for the evaluation of long-term longitudinal safety data and data in groups of 6-week intervals (weeks 1-6, 7-12, etc; total pooled group [PG3] only) after initiating treatment with efgartigimod.

The analysis distinguishes 2 groups: those who received efgartigimod PH20 SC without interruption in Stage B of ARGX-113-1802 (group 1) and those who received efgartigimod PH20 SC in Stage A and were randomized to placebo (withdrawal) in Stage B (group 2). Specifically, the data are presented as follows (Figure 43):

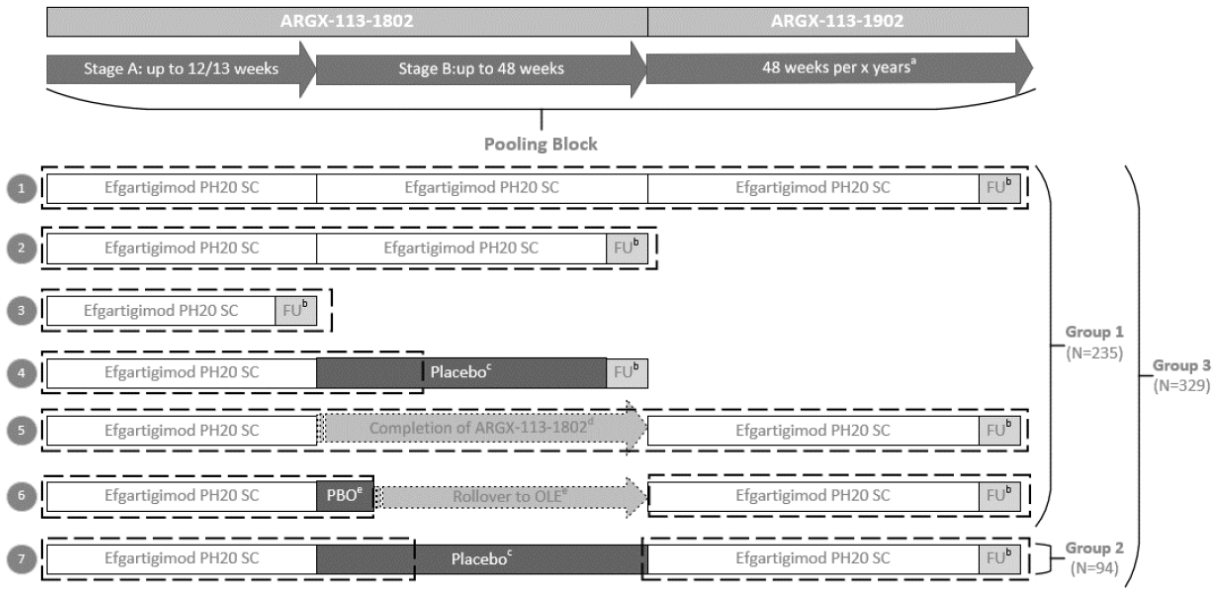
• Group 1 (PG1): Participants who continuously received efgartigimod PH20 SC (ie, they participated in Stage A of ARGX-113-1802).

• Group 2 (PG2): participants who received placebo for more than 2 weeks in ARGX-113-1802 Stage B and received efgartigimod PH20 SC in ARGX-113-1902 (situation 7 in Figure 43). For these participants, data from ARGX-113-1802 Stage A and data from ARGX-113-1902 will be combined.

• Group 3 (PG3, total pooled group): participants who received efgartigimod PH20 SC at any time in ARGX-113-1802 or ARGX-113-1902 (sum of PG1 and PG2)

A conservative approach has been taken by including safety data up to 60 days after the last efgartigimod PH20 SC injection in situations 4 and 7 in Figure 43. In the context of the pooled analysis, IMP-related AEs and AEs leading to IMP discontinuation or interruption occurring in these 60 days are attributed to efgartigimod PH20 SC. To further characterize the safety during those 60 days, additional analyses were performed on the SAEs and AESIs occurring within this 60-day period.

Figure 43: Pooling Block Including All Participants With CIDP Who Received Efgartigimod



CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; FU=follow-up; OLE=open-label extension; PB=pooling block; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Note: safety data collected during the time frame indicated by the dashed boxes are included in the PB.
a Renewable 48-week treatment cycles up to 2 years after marketing authorization in the participant's local country or until efgartigimod PH20 SC becomes commercially available for patients with CIDP or available via a continued access program, whichever comes first.
b Safety data until the date of last contact, date of last efgartigimod administration plus 60 days, or data cutoff date, whichever occurred first, are included in the PB.
c In the PB, data up to 60 days after the last efgartigimod PH20 SC administration are included.
d Participants who directly rolled over from Stage A of ARGX-113-1802 to ARGX-113-1902 upon completion of ARGX-113-1802 (ie, 88th event).
e Participants who received a maximum of 2 weeks (2 doses) of placebo before rolling over to ARGX-113-1902

Overall Extent of Exposure

Study ARGX-113-1802 (Overall Population)

In Stage A, 322 participants in the SAF-A received at least 1 dose or part of a dose of efgartigimod PH20 SC. The mean (SD) duration of treatment was 5.2 (3.28) weeks. The median (min, max) number of efgartigimod PH20 SC administrations was 4.0 (1, 13).

In total, 101 (31.4%) participants were withdrawn from the study during Stage A, and 221 (68.6%) participants were randomized 1:1 in Stage B.

In Stage B, 111 participants in the SAF-B received efgartigimod PH20 SC and 110 participants received placebo. The mean (SD) treatment duration was longer in the efgartigimod PH20 SC arm than in the placebo arm (25.1 [17.17] and 18.7 [16.88] weeks, respectively). The median (min, max) number of IMP administrations per participant was 22.0 (2.0, 48.0) and 12.0 (2.0, 48.0) in the efgartigimod PH20 SC and placebo arms, respectively.

When the 88th event of clinical deterioration in Stage B occurred, 64 (57.7%) participants in the efgartigimod PH20 arm had completed 48 weeks of treatment or had an event in Stage B, 35 (31.5%) participants were ongoing, and 12 (10.8%) participants had withdrawn from the study during Stage B. In the placebo arm, 74 (67.3%) participants had completed 48 weeks of IMP administration or had an event in Stage B, 26 (23.6%) participants were ongoing, and 10 (9.1%) had withdrawn from the study during Stage B. In addition, at the time of the 88th event, 7 (2.3%) participants were ongoing in the run-in period.

Study ARGX-113-1802 (Pretreated population)

In Stage A, 139 participants in the pretreated population in SAF-A received at least 1 dose or part of a dose of efgartigimod PH20 SC. The mean (SD) duration of treatment was 4.8 (3.06) weeks. The median (min, max) number of efgartigimod PH20 SC administrations was 4.0 (1, 13).

In total, 44 (31.7%) participants in the pretreated population were withdrawn from the study during Stage A and 95 (68.3%) participants were randomized 1:1 in Stage B, in which 48 of these participants received efgartigimod PH20 SC and 47 participants received placebo PH20 SC.

The mean (SD) treatment duration was longer in the efgartigimod PH20 SC arm than in the placebo arm (25.1 [16.87] and 13.2 [14.13] weeks, respectively). The median (min, max) number of IMP administrations per participant was 22.5 (2, 48) and 6.0 (2, 48) in the efgartigimod PH20 SC and placebo arms, respectively.

Study ARGX-113-1902

As of the clinical data cutoff date (15 Jun 2023), 228 participants had received at least 1 dose or part of a dose of efgartigimod PH20 SC: 29 participants who rolled over from the 1802 Run-in/Stage A EFG PH20 SC group, 99 from the 1802 Stage B EFG PH20 SC group, and 100 from the 1802 Stage B PBO group. The mean (SD) duration of treatment was 29.92 (30.171) weeks. The median (min, max) number of efgartigimod PH20 SC administrations was 17.0 (1, 136).

Three (1.3%) participants completed the study, 29 (12.7%) participants were withdrawn from the study, and 196 (86.0%) participants were ongoing in the study. The most common reasons for efgartigimod PH20 SC discontinuation were withdrawal by participant and AE (in 9 [3.9%] participants each).

Pooled Safety Data Set

In the total pooled group, 148 (45.0%) participants received at least 6 months of efgartigimod PH20 SC treatment, and 87 (26.4%) participants received at least 12 months of efgartigimod PH20 SC treatment (Table 41).

Table 41: SC Pooling Block: Duration of Treatment (Safety Analysis Set)

Treatment duration	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)	PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)	PG3: Total pooled group (N=329; PYFU=250.3)
≥6 months	93 (39.6)	55 (58.5)	148 (45.0)
≥12 months	56 (23.8)	31 (33.0)	87 (26.4)

efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; PBO PH20 SC=placebo coformulated with rHuPH20 for subcutaneous administration; ISS=integrated summary of safety; N=number of participants in the safety analysis set per pooling group; n=number of participants with at least 6/12 months of treatment; PBO=placebo; PBO PH20 SC=participants who received placebo for more than 2 weeks in Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Note: PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Adverse events

Studies ARGX-113-1802 and ARGX-113-1902

For ARGX-113-1802 and ARGX-113-1902, an overview of AEs in each treatment group is provided below.

Table 42: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Overview of Adverse Events (Safety Analysis Set)

	Study ARGX-113-1802									Study ARGX-113-1902		
	Stage A			Stage B								
	Efgartigimod PH20 SC (N=322; PYFU=46.9)			Efgartigimod PH20 SC (N=111; PYFU=56.7)			Placebo (N=110; PYFU=42.1)			Total (N=228; PYFU=137.43)		
	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AE	204 (63.4)	630	1343.1	71 (64.0)	197	347.6	62 (56.4)	215	510.9	131 (57.5)	481	350.0
≥1 SAE	21 (6.5)	24	51.2	6 (5.4)	8	14.1	6 (5.5)	8	19.0	21 (9.2)	35	25.5
≥1 Grade ≥3 AE	25 (7.8)	29	61.8	7 (6.3)	8	14.1	7 (6.4)	9	21.4	25 (11.0)	44	32.0
≥1 AESI	44 (13.7)	57	121.5	35 (31.5)	43	75.9	37 (33.6)	53	125.9	73 (32.0)	103	74.9
≥1 Injection-related reactions	64 (19.9)	115	245.2	11 (9.9)	18	31.8	6 (5.5)	7	16.6	20 (8.8)	42	30.6
≥1 Injection-site reactions	62 (19.3)	124	264.3	16 (14.4)	22	38.8	7 (6.4)	9	21.4	22 (9.6)	48	34.9
≥1 Fatal AE	2 (0.6)	2	4.3	0	…	…	1 (0.9)	1	2.4	1 (0.4)	1	0.7
≥1 Treatment-related AE	101 (31.4)	260	554.3	27 (24.3)	61	107.6	22 (20.0)	65	154.4	54 (23.7)	119	86.6
≥1 Treatment-related SAE	4 (1.2)	4	8.5	0	…	…	4 (3.6)	5	11.9	3 (1.3)	4	2.9
≥1 Procedure-related AE	33 (10.2)	66	140.7	8 (7.2)	12	21.2	3 (2.7)	5	11.9	11 (4.8)	18	13.1
≥1 AE for which the IMP was discontinued	22 (6.8)	22	46.9	3 (2.7)	3	5.3	1 (0.9)	1	2.4	9 (3.9)	12	8.7
≥1 AE for which the IMP was interrupted	11 (3.4)	15	32.0	18 (16.2)	23	40.6	21 (19.1)	25	59.4	40 (17.5)	48	34.9

AE=adverse event; AESI=adverse event of special interest; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; ECI=evidence of clinical improvement; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ER=event rate; IA=interim analysis; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ⩾1 event; PYFU=participant years of follow-up; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class
Notes: ARGX-113-1802 was conducted in 2 stages: Stage A and Stage B. Participants eligible for Stage A received open-label weekly SC administrations of efgartigimod PH20 SC for up to 12 weeks. During Stage A, participants were monitored for ECI. Participants who fulfilled the criteria for ECI at 2 consecutive visits (confirmed ECI status), rolled over to the randomized-withdrawal, placebo-controlled Stage B. In Stage B, the participants were dosed with efgartigimod PH20 SC or placebo weekly for 48 weeks. Participants who completed week 48 or participants who had reached the primary endpoint (clinical deterioration on the adjusted Inflammatory Neuropathy Cause and Treatment score compared to Stage B baseline) or participants who were in the run-in period, Stage A or Stage B at the time the primary endpoint was reached were allowed to roll over to the open-label extension study ARGX-113-1902.
ER was calculated as the number of events ×100 divided by the PYFU. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years. Unless specified, all AEs were treatment-emergent. Treatment/procedure-related was defined as at least possibly related, or a missing relatedness, to efgartigimod PH20 SC/the procedure, according to the investigator. An AESI was defined as any AE in the MedDRA SOC *Infections and infestations*. Injection-related reactions were defined as AEs in the SMQ (broad) for *Hypersensitivity*, *Anaphylactic reaction*, and *Extravasation* (excluding implants) that occurred within 48 hours of an injection, or within 2 days of the event if no start time was available. Injection-site reactions were defined as all AEs with MedDRA high-level term *Injection site reactions* regardless of the time of AE onset relative to an injection.

Pooled Safety Data Set

An overview of AEs in the pooled safety data set is provided in Table 43.

Table 43: SC Pooling Block: Overview of Adverse Events (Safety Analysis Set)

	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)			PG2: Efgartigimod PH20 SC[a] (PBO PH20 SC) (N=94; PYFU=95.2)			PG3: Total pooled group[a] (N=329; PYFU=250.3)		
	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AE	191 (81.3)	893	575.9	77 (81.9)	490	514.7	268 (81.5)	1383	552.6
≥1 SAE	37 (15.7)	46	29.7	14 (14.9)	25	26.3	51 (15.5)	71	28.4
≥1 Grade ≥3 AE	39 (16.6)	51	32.9	20 (21.3)	33	34.7	59 (17.9)	84	33.6
≥1 AESI	88 (37.4)	135	87.1	46 (48.9)	86	90.3	134 (40.7)	221	88.3
≥1 Injection-related reactions	61 (26.0)	124	80.0	24 (25.5)	54	56.7	85 (25.8)	178	71.1
≥1 Injection-site reactions	58 (24.7)	120	77.4	26 (27.7)	80	84.0	84 (25.5)	200	79.9
≥1 Fatal AE	1 (0.4)	1	0.6	1 (1.1)	1	1.1	2 (0.6)	2	0.8
≥1 Treatment-related AE	103 (43.8)	302	194.7	45 (47.9)	163	171.2	148 (45.0)	465	185.8
≥1 Treatment-related SAE	6 (2.6)	6	3.9	4 (4.3)	5	5.3	10 (3.0)	11	4.4
≥1 Procedure-related AE	30 (12.8)	62	40.0	15 (16.0)	37	38.9	45 (13.7)	99	39.6
≥1 AE for which the IMP was discontinued	26 (11.1)	26	16.8	8 (8.5)	11	11.6	34 (10.3)	37	14.8
≥1 AE for which the IMP was interrupted	40 (17.0)	60	38.7	26 (27.7)	33	34.7	66 (20.1)	93	37.2

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; m=number of events; ER=event rate; ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PYFU=participant years of follow-up; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class
Notes: ER was calculated as the number of events x 100 divided by the PYFU. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years. Unless specified, all AEs were treatment-emergent. Treatment/procedure-related was defined as at least possibly related, or a missing relatedness, to efgartigimod PH20 SC/the procedure according to the investigator. An AESI was defined as any AE in the MedDRA SOC *Infections and infestations*. Injection-related reactions were defined as AEs in the SMQ (broad) for *Hypersensitivity*, *Anaphylactic reaction*, and *Extravasation* (excluding implants) that occurred within 48 hours of an injection, or within 2 days of the event if no start time was available. Injection-site reactions were defined as all AEs with MedDRA high-level term *Injection site reactions* regardless of the time of AE onset relative to an injection.
a AEs with onset ⩽60 days after the last efgartigimod PH20 SC dose and an increased CTCAE grade or severity, and/or a changed relationship to the IMP >60 days after the last efgartigimod PH20 SC dose are not included in the pooling

Common Adverse Events

Studies ARGX-113-1802 and ARGX-113-1902

Common AEs (≥5% of the participants in any treatment group) by MedDRA PT that occurred in ARGX-113-1802 and ARGX-113-1902 are summarized below.

Table 44: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Common (⩾5% of Participants in any Treatment Group) AEs by MedDRA SOC and PT (Safety Analysis Set)

	Study ARGX-113-1802									Study ARGX-113-1902		
	Stage A			Stage B								
	Efgartigimod PH20 SC (N=322; PYFU=46.9)			Efgartigimod PH20 SC (N=111; PYFU=56.7)			Placebo (N=110; PYFU=42.1)			Total (N=228; PYFU=137.43)		
System Organ Class Preferred Term	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AE	204 (63.4)	630	1343.1	71 (64.0)	197	347.6	62 (56.4)	215	510.9	131 (57.5)	481	350.0
General disorders and administration site conditions	81 (25.2)	166	353.9	24 (21.6)	35	61.8	13 (11.8)	22	52.3	32 (14.0)	62	45.1
Injection site bruising	4 (1.2)	5	10.7	6 (5.4)	6	10.6	1 (0.9)	1	2.4	6 (2.6)	7	5.1
Injection site erythema	33 (10.2)	53	113.0	6 (5.4)	6	10.6	0	…	…	7 (3.1)	14	10.2
Infections and infestations	44 (13.7)	57	121.5	35 (31.5)	43	75.9	37 (33.6)	53	125.9	73 (32.0)	103	74.9
COVID-19	7 (2.2)	8	17.1	19 (17.1)	20	35.3	14 (12.7)	14	33.3	31 (13.6)	31	22.6
Upper respiratory tract infection	11 (3.4)	12	25.6	2 (1.8)	3	5.3	11 (10.0)	11	26.1	14 (6.1)	17	12.4
Nervous system disorders	45 (14.0)	66	140.7	8 (7.2)	11	19.4	10 (9.1)	12	28.5	24 (10.5)	40	29.1
Chronic inflammatory demyelinating polyradiculoneuropathy	17 (5.3)	19	40.5	1 (0.9)	1	1.8	1 (0.9)	1	2.4	5 (2.2)	8	5.8
Headache	16 (5.0)	28	59.7	4 (3.6)	6	10.6	2 (1.8)	2	4.8	8 (3.5)	12	8.7

AE=adverse event; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ER=event rate; IA=interim analysis; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ⩾1 event; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class

Notes: ER was calculated as the number of events x 100 divided by the PYFU. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years. Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022).

Pooled Safety Data Set

A tabulation of common AEs (≥5% of the participants in the total group) in the pooled safety data set by MedDRA SOC and PT is provided below.

Table 45: SC Pooling Block: Common (⩾5% of Participants in the Total Group) AEs by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)			PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)			PG3: Total pooled group (N=329; PYFU=250.3)		
	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AE	191 (81.3)	893	575.9	77 (81.9)	490	514.7	268 (81.5)	1383	552.6
General disorders and administration site conditions	77 (32.8)	182	117.4	32 (34.0)	90	94.5	109 (33.1)	272	108.7
Injection site erythema	31 (13.2)	50	32.2	10 (10.6)	23	24.2	41 (12.5)	73	29.2
Injection site pain	13 (5.5)	22	14.2	4 (4.3)	4	4.2	17 (5.2)	26	10.4
Infections and infestations	88 (37.4)	135	87.1	46 (48.9)	86	90.3	134 (40.7)	221	88.3
COVID-19	39 (16.6)	42	27.1	18 (19.1)	18	18.9	57 (17.3)	60	24.0
Nasopharyngitis	12 (5.1)	13	8.4	5 (5.3)	6	6.3	17 (5.2)	19	7.6
Upper respiratory tract infection	17 (7.2)	20	12.9	14 (14.9)	18	18.9	31 (9.4)	38	15.2
Musculoskeletal and connective tissue disorders	45 (19.1)	63	40.6	25 (26.6)	38	39.9	70 (21.3)	101	40.4
Arthralgia	12 (5.1)	13	8.4	7 (7.4)	8	8.4	19 (5.8)	21	8.4
Nervous system disorders	54 (23.0)	84	54.2	20 (21.3)	41	43.1	74 (22.5)	125	49.9
Chronic inflammatory demyelinating polyradiculoneuropathy	21 (8.9)	22	14.2	3 (3.2)	6	6.3	24 (7.3)	28	11.2
Headache	19 (8.1)	36	23.2	4 (4.3)	11	11.6	23 (7.0)	47	18.8

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; ER=event rate; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class

Notes: ER was calculated as the number of events x 100 divided by the PYFU. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years. Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022).

Pretreated population

An overview of AEs in the overall and pretreated populations is presented for Stage A and Stage B in Table 46 and Table 47, respectively.

Table 46: Overview of AE Categories and Common (⩾5% Participants in the Overall or Pretreated Populations) AEs by MedDRA PT or AE Subcategory in the Overall and Pretreated Populations in Stage A of ARGX-113-1802 (SAF-A)

AE category Preferred Term or AE subcategory	Overall population Efgartigimod PH20 SC (N=322; PYFU=46.9) n (%)	m	ER/100 PYFU	Pretreated population Efgartigimod PH20 SC (N=139; PYFU=18.7) n(%)	m	ER/100 PYFU
≥1 AE	204 (63.4)	630	1343.1	92 (66.2)	270	1447.5
Injection site erythema	33 (10.2)	53	113.0	12 (8.6)	14	75.1
Chronic inflammatory demyelinating polyradiculoneuropathy	17 (5.3)	19	40.5	7 (5.0)	9	48.2
Headache	16 (5.0)	28	59.7	6 (4.3)	9	48.2
≥1 SAE	21 (6.5)	24	51.2	7 (5.0)	10	53.6
≥1 Grade 3 or higher AE	25 (7.8)	29	61.8	11 (7.9)	15	80.4
≥1 AESI	44 (13.7)	57	121.5	18 (12.9)	23	123.3
≥1 Injection-related reaction	64 (19.9)	115	245.2	30 (21.6)	42	225.2
Injection site erythema	27 (8.4)	46	98.1	9 (6.5)	11	59.0
≥1 Injection-site reaction	62 (19.3)	124	264.3	27 (19.4)	42	225.2
Injection site erythema	33 (10.2)	53	113.0	12 (8.6)	14	75.1
≥1 Treatment-related injection-site reaction according to PI	57 (17.7)	118	251.6	24 (17.3)	39	209.1
≥1 Procedure-related injection-site reaction according to PI	26 (8.1)	57	121.5	13 (9.4)	17	91.1
≥1 Injection-site reaction for which IMP was discontinued	1 (0.3)	1	2.1	0	…	…
≥1 Fatal AE	2 (0.6)	2	4.3	2 (1.4)	2	10.7
≥1 Treatment-related AE according to PI	101 (31.4)	260	554.3	43 (30.9)	96	514.7
Injection site erythema	32 (9.9)	52	110.9	11 (7.9)	13	69.7
≥1 Treatment-related SAE	4 (1.2)	4	8.5	2 (1.4)	2	10.7
≥1 Procedure-related AE according to PI	33 (10.2)	66	140.7	15 (10.8)	20	107.2
Injection site erythema	13 (4.0)	26	55.4	7 (5.0)	7	37.5
≥1 AE for which IMP was discontinued	22 (6.8)	22	46.9	8 (5.8)	8	42.9
≥1 AE for which IMP was interrupted	11 (3.4)	15	32.0	3 (2.2)	6	32.2

AE=adverse event; AESI=adverse event of special interest; CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ER=event rate; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants per treatment arm in SAF-A; n=number of participants with event; PI=Principal Investigator; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class

Notes: ER was calculated as the number of events × 100 divided by PYFU. PYFU was calculated as the sum of the follow-up times in Stage A of all participants, expressed in years. Unless specified, all AEs were treatment-emergent. Treatment-related was defined as at least possibly related to IMP, according to the investigator, or a missing relatedness. Procedure-related was defined as at least possibly related to study procedures according to the investigator or a missing relatedness. An AESI was defined as any AE in the MedDRA SOC Infections and infestations. Injection-related reactions were defined as AEs in the SMQ (broad) for Hypersensitivity, Anaphylactic reaction, and Extravasation (excluding implants) that occurred within 48 hours of an injection, or within 2 days of the event if no start time was available. Injection-site reactions were defined as all AEs with MedDRA high-level term Injection site reactions regardless of the time of AE onset relative to an injection. The denominator for the percentage calculations was the total number of participants in SAF-A

The pretreated population includes participants in ARGX-113-1802 who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening.

Table 47: Overview of AE Categories and Common (⩾5% Participants in any Treatment Arm in the Overall or Pretreated Populations) AEs by MedDRA PT or AE Subcategory in the Overall and Pretreated Populations in Stage B of ARGX-113-1802 (SAF-B)

AE category Preferred Term or AE subcategory	Overall population						Pretreated population					
	Efgartigimod PH20 SC (N=111; PYFU=56.7)			Placebo (N=110; PYFU=42.1)			Efgartigimod PH20 SC (N=48; PYFU=24.2)			Placebo (N=47; PYFU=12.9)		
	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AE	71 (64.0)	197	347.6	62 (56.4)	215	510.9	36 (75.0)	111	458.0	27 (57.4)	67	517.7
COVID-19	19 (17.1)	20	35.3	14 (12.7)	14	33.3	9 (18.8)	10	41.3	4 (8.5)	4	30.9
Nasopharyngitis	5 (4.5)	5	8.8	3 (2.7)	3	7.1	5 (10.4)	5	20.6	0	...	...
Influenza like illness	3 (2.7)	3	5.3	0	…	…	3 (6.3)	3	12.4	0	…	…
Injection site erythema	6 (5.4)	6	10.6	0	…	…	3 (6.3)	3	12.4	0	...	...
Upper respiratory tract infection	2 (1.8)	3	5.3	11 (10.0)	11	26.1	2 (4.2)	3	12.4	5 (10.6)	5	38.6
Injection site bruising	6 (5.4)	6	10.6	1 (0.9)	1	2.4	2 (4.2)	2	8.3	0	…	…
≥1 SAE	6 (5.4)	8	14.1	6 (5.5)	8	19.0	1 (2.1)	1	4.1	4 (8.5)	6	46.4
≥1 Grade 3 or higher AE	7 (6.3)	8	14.1	7 (6.4)	9	21.4	2 (4.2)	2	8.3	4 (8.5)	6	46.4
≥1 AESI	35 (31.5)	43	75.9	37 (33.6)	53	125.9	21 (43.8)	27	111.4	16 (34.0)	23	177.7
COVID-19	19 (17.1)	20	35.3	14 (12.7)	14	33.3	9 (18.8)	10	41.3	4 (8.5)	4	30.9
Nasopharyngitis	5 (4.5)	5	8.8	3 (2.7)	3	7.1	5 (10.4)	5	20.6	0	…	…
Upper respiratory tract infection	2 (1.8)	3	5.3	11 (10.0)	11	26.1	2 (4.2)	3	12.4	5 (10.6)	5	38.6
≥1 Injection-related reaction	11 (9.9)	18	31.8	6 (5.5)	7	16.6	6 (12.5)	11	45.4	4 (8.5)	4	30.9
Injection site erythema	5 (4.5)	5	8.8	0	…	…	3 (6.3)	3	12.4	0	…	…
Injection site bruising	6 (5.4)	6	10.6	1 (0.9)	1	2.4	2 (4.2)	2	8.3	0	…	…
Injection site erythema	6 (5.4)	6	10.6	0	…	…	3 (6.3)	3	12.4	0	…	…
≥1 Treatment-related injection-site reaction according to PI	13 (11.7)	17	30	5 (4.5)	5	11.9	7 (14.6)	11	45.4	3 (6.4)	3	23.2
≥1 Procedure-related injection-site reaction according to PI	8 (7.2)	12	21.2	3 (2.7)	5	11.9	4 (8.3)	7	28.9	0	…	…
≥1 Fatal AE	0	…	…	1 (0.9)	1	2.4	0	…	…	1 (2.1)	1	7.7
≥1 Treatment-related AE according to PI	27 (24.3)	61	107.6	22 (20.0)	65	154.4	16 (33.3)	39	160.9	12 (25.5)	20	154.5
Injection site erythema	6 (5.4)	6	10.6	0	…	…	3 (6.3)	3	12.4	0	…	…
≥1 Treatment-related SAE	0	…	…	4 (3.6)	5	11.9	0	…	…	4 (8.5)	5	38.6
≥1 Procedure-related AE according to PI	8 (7.2)	12	21.2	3 (2.7)	5	11.9	4 (8.3)	7	28.9	0	…	…
≥1 AE for which IMP was discontinued	3 (2.7)	3	5.3	1 (0.9)	1	2.4	0	…	…	1 (2.1)	1	7.7
≥1 AE for which IMP was interrupted	18 (16.2)	23	40.6	21 (19.1)	25	59.4	11 (22.9)	13	53.6	7 (14.9)	9	69.5
COVID-19	11 (9.9)	11	19.4	13 (11.8)	13	30.9	6 (12.5)	6	24.8	4 (8.5)	4	30.9

AE=adverse event; AESI=adverse event of special interest; CDAS=CIDP Disease Activity Status; CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ER=event

rate; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants per treatment arm in SAF-B; n=number of participants with event; PI=Principal Investigator; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; SAF-B=Stage B safety analysis set; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class
Notes: ER was calculated as the number of events × 100 divided by PYFU. PYFU was calculated as the sum of the follow-up times in Stage B of all participants per treatment arm, expressed in years. Unless specified, all AEs were treatment-emergent. Treatment-related was defined as at least possibly related to IMP, according to the investigator, or a missing relatedness. Procedure-related was defined as at least possibly related to study procedures according to the investigator or a missing relatedness. An AESI was defined as any AE in the MedDRA SOC Infections and infestations. Injection-related reactions were defined as AEs in the SMQ (broad) for Hypersensitivity, Anaphylactic reaction, and Extravasation (excluding implants) that occurred within 48 hours of an injection, or within 2 days of the event if no start time was available. Injection-site reactions were defined as all AEs with MedDRA high-level term Injection site reactions regardless of the time of AE onset relative to an injection. The denominator for the percentage calculations was the total number of participants per treatment arm in SAF-B.
The pretreated population includes participants in ARGX-113-1802 who received CIDP therapy within 6 months before screening and had a CDAS score of ⩾4 at screening

Serious adverse event/deaths/other significant events

Deaths

Across the CIDP efgartigimod clinical program (clinical data cutoff 15 Jun 2023), 4 fatal AEs occurred in participants who had received efgartigimod PH20 SC. Of the 4 deaths, 3 SAEs leading to death started ⩽60 days after the last efgartigimod PH20 SC dose and 1 SAE started >60 days after the last efgartigimod PH20 SC dose. A by-participant summary of fatal AEs is provided in Table 48 and briefly summarised below.

Table 48: Overview of Deaths

Participant No. (Study and treatment)	Fatal AE (PT)	Number of days between last efgartigimod dose and SAE onset[a]	Number of days between last efgartigimod dose and death	Number of efgartigimod doses received before the death	Investigator causality assessment	Sponsor causality assessment
SAEs leading to death starting ≤60 days after the last efgartigimod PH20 SC dose						
[redacted][b] (ARGX-113-1802 Stage A)	Cardiac arrest	14	14	2 doses in ARGX-113-1802 Stage A	Not related	Not related
[redacted][b] (ARGX-113-1802 Stage A follow-up)	Chronic inflammatory demyelinating polyradiculoneuropathy	37	117	2 doses in ARGX-113-1802 Stage A	Not related	Not related
[redacted] (ARGX-113-1902 - 1802 Stage B PBO PH20 SC)	Chronic inflammatory demyelinating polyradiculoneuropathy	2	26	43 doses in ARGX-113-1902 6 doses in ARGX-113-1802 Stage A	Related	Not related
SAEs leading to death starting >60 days after the last efgartigimod PH20 SC dose						
[redacted][b] (ARGX-113-1802 Stage B – PBO)	Pneumonia	282	284	4 doses in ARGX-113-1802 Stage A	Related	Not related

AE=adverse event; AESI=adverse event of special interest; CIDP=chronic inflammatory demyelinating polyneuropathy; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; IMP=investigational medicinal product; PBO=placebo; PT=Preferred Term; SAE=serious adverse event; SC=subcutaneous(ly)
a The onset dates were calculated as AE start date/date of death – date of last efgartigimod administration before the AE/death occurred + 1 day.
b Participant in the pretreated population (ie, received CIDP therapy within 6 months before screening for ARGX-113-1802 and had a CDAS score of ⩾4 at screening) of ARGX-113-1802

Serious Adverse Events

Studies ARGX-113-1802

In Stage A, 24 SAEs occurred in 21 (6.5%; 51.2 events/100 PYFU) participants. Except for CIDP (14 [4.3%] participants), all SAEs by PT occurred in 1 (0.3%) participant each. SAEs assessed as related to efgartigimod PH20 SC by the investigator occurred in 4 (1.2%) participants and included CIDP in 2

participants, Clostridium difficile colitis in 1 participant, and Squamous cell carcinoma of skin in 1 participant.

In Stage B, 8 SAEs occurred in 6 (5.4%; 14.1 events/100 PYFU) participants in the efgartigimod PH20 SC arm and 8 SAEs occurred in 6 (5.5%; 19.0 events/100 PYFU) participants in the placebo arm. Except for Pneumonia (0 and 2 [1.8%] participants in the efgartigimod PH20 SC and placebo arms, respectively, all SAEs by PT occurred in 1 (0.9%) participant each in either arm.

No participants had SAEs assessed as related to efgartigimod PH20 SC by the investigator. IMP-related SAEs occurred in 4 (3.6%) participants in the placebo arm, 1 of whom died (2 SAEs [1 grade 4 and 1 fatal] of Pneumonia). Other IMP-related SAEs included CIDP, deafness unilateral, and Pneumonia, each reported in 1 participant.

A similar profile and frequency of the SAEs by PT was observed in the pretreated population (Serious Adverse Events) compared with the overall population in ARGX-113-1802.

Study ARGX-113-1902

In the total group of ARGX-113-1902, 35 SAEs occurred in 21 (9.2%; 25.5 events/100 PYFU) participants. The percentage of participants with ≥1 SAE was similar between the 1802 Stage B PBO and 1802 Stage B EFG PH20 SC groups (11 [11.0%] and 8 [8.1%], respectively); however, the event rate was higher in the 1802 Stage B PBO group than the 1802 Stage B EFG PH20 SC group (29.3 events/100 PYFU and 15.6 events/100 PYFU, respectively).

None of the SAEs by PT occurred in ≥5% of the participants in the total group. All SAEs by PT occurred in 1 participant, except for CIDP (5 [2.2%] participants), COVID-19 (3 [1.3%] participants), and Fall (2 [0.9%] participants). SAEs assessed as related to efgartigimod PH20 SC by the investigator occurred in 3 (1.3%; 2.9 events/100 PYFU) participants and included CIDP, Lymphadenitis, and Urinary tract infection.

Pooled Safety Data Set

A tabulation of SAEs that occurred in ≥5% of the participants in the total pooled group by MedDRA SOC and PT is provided in Table 49.

In the total pooled group, 71 SAEs occurred in 51 (15.5%; 28.4 events/100 PYFU) participants. SAEs considered related to efgartigimod PH20 SC occurred in 10 (3.0%) participants.

At the PT level, CIDP (6.1%), was the only SAE that occurred in ≥5% of the participants in the total pooled group. Other SAEs occurring in more than 1 participant in the total pooled group were COVID-19 in 4 (1.2%) participants, and COVID-19 pneumonia, Pneumonia, and Fall, each in 2 (0.6%) participants. All other SAEs by PT occurred in 1 participant.

Analysis of SAEs by 6-week intervals for participants with at least 6 or 12 months of treatment showed that longer efgartigimod PH20 SC exposure was not associated with a higher frequency of SAEs: there were no more than 4 participants with an SAE in any 6-week interval through weeks 151 to 156 in the cohort of participants with at least 6 months of treatment and no more than 1 participant with an SAE at any 6-week interval in the cohort of participants with at least 12 months of treatment. There were no trends in the occurrence of SAEs by PT.

Table 49: SC Pooling Block: SAEs (⩾5% of Participants in the Total Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)		PG3: Total pooled group (N=329; PYFU=250.3)	
	n (%)	m	n (%)	m	n (%)	m
≥1 SAE	37 (15.7)	46	14 (14.9)	25	51 (15.5)	71
Nervous system disorders	18 (7.7)	19	4 (4.3)	7	22 (6.7)	26
Chronic inflammatory demyelinating polyradiculoneuropathy	17 (7.2)	18	3 (3.2)	5	20 (6.1)	23

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Adverse Events of Special Interest

Because efgartigimod causes a reduction in total IgG levels, the risk of infections may be increased. Therefore, AEs in the MedDRA SOC Infections and infestations have been defined as AESIs in most phase 2 and 3 clinical studies of efgartigimod PH20 SC. All PTs in the SOC Infections and infestations were retrieved for analysis of infections.

Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902

A summary table of common AESIs (≥5% of the participants in any treatment group) in ARGX-113-1802 and ARGX-113-1902, by MedDRA SOC and PT, is presented in table 50.

Table 50: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: AESIs (⩾5% of Participants in Any Treatment Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	Study ARGX-113-1802						Study ARGX-113-1902	
	Stage A		Stage B					
	Efgartigimod PH20 SC (N=322; PYFU=46.9)		Efgartigimod PH20 SC (N=111; PYFU=56.7)		Placebo (N=110; PYFU=42.1)		Total (N=228; PYFU=137.43)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AESI	44 (13.7)	57	35 (31.5)	43	37 (33.6)	53	73 (32.0)	103
COVID-19	7 (2.2)	8	19 (17.1)	20	14 (12.7)	14	31 (13.6)	31
Upper respiratory tract infection	11 (3.4)	12	2 (1.8)	3	11 (10.0)	11	14 (6.1)	17

AE=adverse event; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ⩾1 event; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). An AESI was defined as any AE in the MedDRA SOC Infections and infestations. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Pooled Safety Data Set

A summary of AESIs (AEs in the SOC Infections and infestations) that occurred in ≥5% of the participants in the total pooled group is presented by PT in Table 51.

AESIs occurred in 134 (40.7%) participants. Analysis by 6-week intervals showed that for participants with at least 6 or 12 months of treatment prolonged exposure to efgartigimod PH20 SC was not associated with an increased rate of AESIs of infection or different types of infection.

The most common (≥5% participants in the total group) AESIs by PT were COVID-19, Nasopharyngitis, and Upper respiratory tract infection. There were no opportunistic infections reported (SMQ [narrow] for Opportunistic infections was used).

One fatal SAE of Pneumonia occurred in a participant in the ARGX-113-1802 Stage B, placebo arm. No other fatal AESIs occurred.

Serious AESIs occurred in 12 (3.6%) participants in the total pooled group. None of the serious AESIs occurred in ≥5% of the participants. Overall, 4 (1.2%) participants had serious AESIs of COVID-19, serious AESIs of COVID-19 pneumonia and Pneumonia, each occurred in 2 (0.6%) participants each.

By worst severity, most participants in the total group had AESIs of grade 1 (59 [17.9%] participants) or grade 2 (63 [19.1%] participants). Overall, 9 (2.7%) participants had grade 3 AESIs and 3 (0.9%) participants had grade 4 AESIs.

In the total group, AESIs by PT of grade ≥3 occurred in at most 3 (0.9%) participants and included:

• Grade 4:

– Appendicitis, 1 (0.3%) participant

– COVID-19, 1 (0.3%) participant

– Suspected COVID-19, 1 (0.3%) participant

• Grade 3:

– Clostridium difficile colitis, 1 (0.3%) participant

– COVID-19, 3 (0.9%) participants

– COVID-19 pneumonia, 2 (0.6%) participants

– Pneumonia, 2 (0.6%) participants

– Urinary tract infection, 1 (0.3%) participant

– Wound infection, 1 (0.3%) participant (this participant also had a grade 4 AESI of COVID-19)

AESIs that were considered related to efgartigimod PH20 SC by the investigator occurred in 33 (10.0%) participants. No efgartigimod PH20 SC–related AESIs by PT occurred in ≥5% of the participants. The most common efgartigimod PH20 related SAEs were Upper respiratory tract infection (13 [4.0%]), COVID-19 (5 [1.5%]), and Urinary tract infection (5 [1.5%]). Other efgartigimod PH20 SC–related AESIs occurred in at most 2 participants in the total pooled group.

The median (min, max) time to first AESI onset was 85.0 (1, 623) days. First AESI onset was defined as the day of first occurrence of any AESI for a participant versus the first administration of efgartigimod PH20 SC in ARGX-113-1802 Stage A.

Table 51: SC Pooling Block: AESIs (⩾5% of Participants in the Total Group) by PT (Safety Analysis Set)

	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)		PG3: Total pooled group (N=329; PYFU=250.3)	
Preferred Term	n (%)	m	n (%)	m	n (%)	m
≥1 AESI	88 (37.4)	135	46 (48.9)	86	134 (40.7)	221
COVID-19	39 (16.6)	42	18 (19.1)	18	57 (17.3)	60
Nasopharyngitis	12 (5.1)	13	5 (5.3)	6	17 (5.2)	19
Upper respiratory tract infection	17 (7.2)	20	14 (14.9)	18	31 (9.4)	38

AESI=adverse event of special interest; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). An AESI was defined as any AE in the MedDRA SOC *Infections and infestations*. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

The incidence of AESIs relative to nadir IgG levels was evaluated. A summary of AESIs in the total group in any nadir IgG quartile is presented by nadir IgG category, SOC, and PT (Table 52). No clear trend was observed across IgG nadir quartiles. The participants in the nadir >P75 quartile had the lowest AESI frequency; however, the event rate was higher than the nadir ≤P25 and P25<nadir≤P50 quartile.

Table 52: SC Pooling Block: AESI (⩾5% of Participants in Any Nadir Group) in the Total Group by Nadir IgG Category and PT (Safety Analysis Set)

	PG3: Total pooled group											
	Nadir ≤P25 (N=80; PYFU=85.8)			P25<Nadir≤P50 (N=81; PYFU=77.1)			P50<Nadir≤P75 (N=79; PYFU=55.9)			Nadir >P75 (N=79; PYFU=30.0)		
Preferred Term	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU	n (%)	m	ER/100 PYFU
≥1 AESI	40 (50.0)	59	68.8	34 (42.0)	68	88.2	38 (48.1)	59	105.5	19 (24.1)	30	99.9
COVID-19	15 (18.8)	16	18.7	12 (14.8)	12	15.6	18 (22.8)	19	34.0	11 (13.9)	12	40.0
Nasopharyngitis	4 (5.0)	4	4.7	8 (9.9)	9	11.7	3 (3.8)	4	7.1	2 (2.5)	2	6.7
Upper respiratory tract infection	9 (11.3)	10	11.7	8 (9.9)	12	15.6	8 (10.1)	10	17.9	5 (6.3)	5	16.7
Urinary tract infection	4 (5.0)	4	4.7	5 (6.2)	7	9.1	3 (3.8)	3	5.4	2 (2.5)	2	6.7

AE=adverse event; AESI=adverse event of special interest; ER=event rate; IgG=immunoglobulin gamma; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants who reported ⩾1 event; N=number of participants in the safety analysis set per nadir IgG category; P25=25th percentile; P50=50th percentile; P75=75th percentile; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; SC=subcutaneous(ly); SOC=System Organ Class

Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Nadir IgG quartiles (mg/L): Q1=1220-2380; Q2=2381-3240; Q3=3241-4500; Q4=4501-19550. An AESI was defined as any AE in the MedDRA SOC *Infections and infestations*. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years. ER was calculated as the number of events × 100 divided by the PYFU

COVID-19–Relevant Events in the Pooled Safety Data Set

No safety concerns associated with efgartigimod PH20 SC treatment were identified based on the review of AEs relevant to COVID-19 infection. The high percentage of participants with COVID-19–related AEs was expected because ARGX-113-1802 and ARGX-113-1902 were conducted during the global COVID-19 pandemic. The study dates (first participant's first visit and last participant's last visit/data cutoff) were 15 Apr 2020 to 11 May 2023 for ARGX-113-1802 and 18 Sep 2020 to 15 Jun 2023 for ARGX-113-1902, which coincide with the start of the pandemic in Q1 2020 and high COVID-19 infection rates.

The following PTs related to COVID-19 infection occurred in the total group:

- 60 AEs of COVID-19 in 57 (17.3%) participants
- 3 AEs of Suspected COVID-19 in 3 (0.9%) participants
- 2 AEs of COVID-19 pneumonia in 2 (0.6%) participants
- 1 AE of Asymptomatic COVID-19 in 1 (0.3%) participant
- 1 AE of Coronavirus infection in 1 (0.3%) participant
- 1 AE of Coronavirus pneumonia in 1 (0.3%) participant
- 1 AE of SARS-CoV-2 test positive in 1 (0.3%) participant

For 5 (1.5%) participants, COVID-19 AEs were considered related to efgartigimod PH20 SC by the investigator. No other COVID-19-related events were considered related to efgartigimod PH20 SC.

Injection-Related Reactions

Injection-related reactions are defined as AEs in the MedDRA SMQ (broad) selection for Hypersensitivity, Anaphylactic reaction, or Extravasation (excluding implants) occurring within 48 hours of an injection or 2 days if no AE start time was available.

Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902

For ARGX-113-1802 and ARGX-113-1902, injection-related reactions that occurred in ≥5% of the participants in any treatment group by MedDRA SOC and PT are presented in Table 53.

Table 53: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Injection-Related Reactions (⩾5% of Participants in Any Treatment Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	Study ARGX-113-1802						Study ARGX-113-1902	
	Stage A		Stage B					
	Efgartigimod PH20 SC (N=322; PYFU=46.9)		Efgartigimod PH20 SC (N=111; PYFU=56.7)		Placebo PH20 SC (N=110; PYFU=42.1)		Total (N=228; PYFU=137.43)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 Injection-related reaction	64 (19.9)	115	11 (9.9)	18	6 (5.5)	7	20 (8.8)	42
General disorders and administration site conditions	47 (14.6)	87	8 (7.2)	8	2 (1.8)	2	9 (3.9)	25
Injection site erythema	27 (8.4)	46	5 (4.5)	5	0	…	6 (2.6)	13

AE=adverse event; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ≥1 event; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SMQ=Standard MedDRA Query; SOC=System Organ Class

Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Injection-related reactions were defined as AEs in the SMQ (broad) for *Hypersensitivity*, *Anaphylactic reaction*, and *Extravasation* (excluding implants) that occurred within 48 hours of an injection or infusion, or within 2 days of the event if no start time was available. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Pooled Safety Data Set

A tabulation of injection-related reactions that occurred in ≥5% of the participants in the total pooled group by MedDRA SOC and PT is provided in Table 54.

Table 54: SC Pooling Block: Injection-Related Reactions (⩾5% of Participants in the Total Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)		PG3: Total pooled group (N=329; PYFU=250.3)	
	n (%)	m	n (%)	m	n (%)	m
≥1 Injection-related reaction	61 (26.0)	124	24 (25.5)	54	85 (25.8)	178
General disorders and administration site conditions	40 (17.0)	75	17 (18.1)	46	57 (17.3)	121
Injection site erythema	25 (10.6)	42	9 (9.6)	22	34 (10.3)	64

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants who reported ⩾1 event; N=number of participants in the safety analysis set per pooling group; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class

Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Injection-related reactions were defined as AEs in the SMQ (broad) for Hypersensitivity, Anaphylactic reaction, and Extravasation (excluding implants) that occurred within 48 hours of an injection or infusion, or within 2 days of the event if no start time was available. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years

Localized Injection-Site Reactions

Injection-site reactions are defined as all AEs with MedDRA high-level term "Injection site reactions" regardless of the time of onset relative to an injection.

Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902

For ARGX-113-1802 and ARGX-113-1902, a tabulation of localized injection-site reactions that occurred in ≥5% of the participants in any treatment group by MedDRA SOC and PT is provided in Table 55.

Table 55: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Localized Injection-Site Reactions (⩾5% of Participants in Any Treatment Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	Study ARGX-113-1802						Study ARGX-113-1902	
	Stage A		Stage B					
	Efgartigimod PH20 SC (N=322; PYFU=46.9)		Efgartigimod PH20 SC (N=111; PYFU=56.7)		Placebo (N=110; PYFU=42.1)		Total (N=228; PYFU=137.43)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 Injection-site reaction	62 (19.3)	124	16 (14.4)	22	7 (6.4)	9	22 (9.6)	48
General disorders and administration site conditions	62 (19.3)	124	16 (14.4)	22	7 (6.4)	9	22 (9.6)	48
Injection site bruising	4 (1.2)	5	6 (5.4)	6	1 (0.9)	1	6 (2.6)	7
Injection site erythema	33 (10.2)	53	6 (5.4)	6	0	…	7 (3.1)	14

AE=adverse event; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ⩾1 event; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Injection-site reactions were defined as all AEs with MedDRA high-level term *Injection site reactions* regardless of the time of AE onset relative to an injection. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Pooled Safety Data Set

Injection-site reactions occurred in 84 (25.5%) participants. Injection-site reactions that occurred in ≥5% of the participants in the total group were Injection site erythema (41 [12.5%]) and Injection site pain (17 [5.2%]) (Table 56)

Table 56: SC Pooling Block: Injection-Site Reactions (⩾5% of Participants in the Total Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)		PG3: Total pooled group (N=329; PYFU=250.3)	
	n (%)	m	n (%)	m	n (%)	m
≥1 Injection-site reaction	58 (24.7)	120	26 (27.7)	80	84 (25.5)	200
General disorders and administration site conditions	58 (24.7)	120	26 (27.7)	80	84 (25.5)	200
Injection site erythema	31 (13.2)	50	10 (10.6)	23	41 (12.5)	73
Injection site pain	13 (5.5)	22	4 (4.3)	4	17 (5.2)	26

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Injection-site reactions were defined as all AEs with MedDRA high-level term *Injection site reactions* regardless of the time of AE onset relative to an injection. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Injection site erythema is the only injection-site reaction that occurred in ≥5% of the participants in any 3-month interval (Table 57).

Table 57: SC Pooling Block: Injection-Site Reactions (⩾5% of Participants in Any 3-Month Interval) in Any 3-Month Interval by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG3: Total pooled group													
	0 to 3 months (N=329)		>3 to 6 months (N=249)		>6 to 9 months (N=161)		>9 to 12 months (N=129)		>12 to 15 months (N=96)		>15 to 18 months (N=76)		>18 to 21 months (N=49)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 Injection-site reaction	73 (22.2)	157	17 (6.8)	35	3 (1.9)	3	0	…	0	…	2 (2.6)	2	2 (4.1)	3
General disorders and administration site conditions	73 (22.2)	157	17 (6.8)	35	3 (1.9)	3	0	…	0	…	2 (2.6)	2	2 (4.1)	3
Injection site erythema	38 (11.6)	62	3 (1.2)	7	2 (1.2)	2	0	…	0	…	0		1 (2.0)	2

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per 3-month interval; n=number of participants who reported ⩾1 event; PG=pooling group; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). Injection-site reactions were defined as all AEs with MedDRA high-level term *Injection site reactions* regardless of the time of AE onset relative to an injection. PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Of the 6 participants with AEs in the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) 5 (1.5%) occurred in participants in the total pooled group. Additionally, 1 participant had an SAE of Lipoma while receiving placebo in ARGX-113-1802 >60 days after the last dose of efgartigimod

PH20 SC. A participant-level summary of the AEs, including links to the narratives for the SAEs, is provided in Table 58.

Participant-level review showed that, except for a participant (aged between 35-55 years) with nonserious Lipoma, all participants were >60 years of age, and the majority (5 of 6 participants) were male. Four participants had a relevant medical history.

Four of the events were SAEs and 3 were grade ≥3. The SAE that occurred during treatment-free follow-up in ARGX-113-1802 was considered possibly related to efgartigimod PH20 SC by the investigator. This participant had a relevant medical history. Additionally, 1 nonserious, grade 1 AE of Lipoma occurred in a participant (aged between 35-55 years) who received prior therapy with IVIg/SCIg and was considered possibly related to efgartigimod PH20 SC by the investigator.

The time between the first and last efgartigimod administration (either in ARGX-113-1802 or ARGX-113-1902) and the AE onset ranged from 90 to 309 days and 4 to 75 days, respectively. Participants had received between 7 and 45 doses of efgartigimod PH20 SC before the onset of the AE.

In the respective age group and patients with related medical history, the occurrence of prostate cancer and transitional cell carcinoma is not uncommon.

Table 58: SC Pooling Block: Overview of AEs Within MedDRA SOC Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

Participant No. (Treatment)	PT	Age[a] (years) Sex (M/F)	Seriousness (Yes/No)	CTCAE severity	Number of days between the first/last dose of efgartigimod and the AE onset[b] Number of efgartigimod doses received	Duration (days)	Investigator causality assessment	Action concerning efgartigimod	Concomitant therapy started because of AE (Yes/No)	Outcome	Relevant medical history (Yes/No)
ARGX-113-1802											
[redacted] (Stage A - FU)	Squamous cell carcinoma	[redacted]	Yes	Gr 2	90/13 12 doses	NA	Pos	Not applicable	No	nRec	Yes [redacted]
[redacted] (Stage B–EFG PH20)	Prostate cancer	[redacted]	Yes	Gr 3	244/6 35 doses	>46	Not	Wit	No	nRec	Yes [redacted] (source: narrative)
[redacted] (Stage B–EFG PH20)	Transitional cell carcinoma	[redacted]	Yes	Gr 4	309/4 45 doses	>43	Not	Wit	No	nRec	Yes [redacted]
[redacted][c] (Stage B–EFG PH20)	Lipoma	[redacted]	No	Gr 1	146/6 21 doses	>219	Pos	No	No	nRec	No
[redacted] (Stage B–PBO)	Lipoma	[redacted]	Yes	Gr 3	117/75 7 doses EFG PH20 SC (Stage A) 10 doses placebo (Stage B)	4	Not	Int	Yes	Rec	No
ARGX-113-1902											
[redacted] (1802 Stage B EFG PH20 SC)	Basal cell carcinoma	[redacted]	No	Gr 2	200/6 28 doses	23	Not	No	No	Rec	Yes [redacted]

AE=adverse event; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; F=female; FU=follow-up; Gr=grade; int=drug interrupted; M=male; NA=not available; No=dose not changed/no concomitant therapy started because of AE; Not=not related; nRec=not recovered; PBO=placebo; Pos=possibly related; PT=Preferred Term; Rec=recovered; SAE=serious adverse event; SC=subcutaneous(ly); wit=drug withdrawn

a The age presented in the table is the one recorded at ARGX-113-1802 Stage A baseline
b The first efgartigimod PH20 intake is the first dose in ARGX-113-1802. The onset dates were calculated as AE start date – date of first/last efgartigimod administration before the AE occurred+ 1 day
c Participant in the pretreated population (ie, received CIDP therapy within 6 months before screening for ARGX-113-1802 and had a CDAS score of ≥4 at screening) of ARGX-113-1802.

Laboratory findings

IgG and serum albumin bind to and recycle via FcRn. FcRn antagonists other than efgartigimod show a reduction in albumin levels. Efgartigimod binds to FcRn at a site distinct from the albumin-binding site of FcRn; efgartigimod is not expected to affect the levels of albumin.

Studies ARGX-113-1802 and ARGX-113-1902

Shifts from baseline to a grade ≥3 abnormality are summarised for ARGX-113-1802 and ARGX-113-1902 in Table 59.

Table 59: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Worst-Case Laboratory Abnormalities of CTCAE Grade 3 and Grade 4 (Safety Analysis Set)

	Study ARGX-113-1802						Study ARGX-113-1902	
	Stage A		Stage B					
	Efgartigimod PH20 SC (N=322)		Efgartigimod PH20 SC (N=111)		Placebo (N=110)		Total (N=228)	
	n/Na	%	n/Na	%	n/Na	%	n/Na	%
Clinical chemistry								
Alanine aminotransferase increased	1/320	0.3	0	…	0	…	1/225	0.4
Grade 3	0	…	0	…	0	…	1/225	0.4
Grade 4	1/320	0.3	0	…	0	…	0	…
Aspartate aminotransferase increased	1/320	0.3	0	…	0	…	1/225	0.4
Grade 3	1/320	0.3	0	…	0	…	1/225	0.4
GGT increased	0	…	0	…	0	…	2/224	0.9
Grade 3	0	…	0	…	0	…	1/224	0.4
Grade 4	0	…	0	…	0	…	1/224	0.4
Hyperkalemia	1/320	0.3	1/110	0.9	0	…	0	…
Grade 3	1/320	0.3	1/110	0.9	0	…	0	…
Hypernatremia	1/320	0.3	0	…	0	…	0	…
Grade 4	1/320	0.3	0	…	0	…	0	…
Hypokalemia	1/320	0.3	0	…	0	…	0	…
Grade 3	1/320	0.3	0	…	0	…	0	…
Hyponatremia	4/320	1.3	1/110	0.9	0	…	0	…
Grade 3	4/320	1.3	1/110	0.9	0	…	0	…
Hematology								
Activated partial thromboplastin time prolonged	2/319	0.6	0	…	0	…	0	…
Grade 3	2/319	0.6	0	…	0	…	0	…
Lymphocyte count decreased	2/320	0.6	0	…	0	…	0	…
Grade 3	1/320	0.3	0	…	0	…	0	…
Grade 4	1/320	0.3	0	…	0	…	0	…
Neutrophil count decreased	4/320	1.3	1/109	0.9	1/105	1.0	1/223	0.4
Grade 3	4/320	1.3	1/109	0.9	0	…	0	…
Grade 4	0	…	0	…	1/105	1.0	1/223	0.4
White blood cell decreased	0	…	0	…	1/105	1.0	0	…
Grade 3	0	…	0	…	1/105	1.0	0	…

CTCAE=Common Terminology Criteria for Adverse Events; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ≥1 event; Na=number of participants in the analysis set and treatment group with data for the parameter; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Note: Unless specified, all clinical laboratory abnormalities were treatment-emergent. The worst-case abnormality is defined as the highest/lowest abnormal post-baseline value that was not present at baseline, considering all post-baseline assessments (including unscheduled assessments).

Pooled Safety Data Set

Worst-case laboratory abnormalities of grade 3 and grade 4 are summarized in Table 60.

Table 60: SC Pooling Block: Worst-Case Laboratory Abnormalities of CTCAE Grade 3 and Grade 4 (Safety Analysis Set)

	PG1: Efgartigimod PH20 SC (only) (N=235)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94)		PG3: Total pooled group (N=329)	
	n/Na	%	n/Na	%	n/Na	%
Clinical chemistry						
Alanine aminotransferase increased	1/231	0.4	1/94	1.1	2/325	0.6
Grade 3	0	…	1/94	1.1	1/325	0.3
Grade 4	1/231	0.4	0	…	1/325	0.3
Aspartate aminotransferase increased	1/231	0.4	1/94	1.1	2/325	0.6
Grade 3	1/231	0.4	1/94	1.1	2/325	0.6
GGT increased	0	…	1/94	1.1	1/325	0.3
Grade 4	0	…	1/94	1.1	1/325	0.3
Hyperkalemia	2/231	0.9	0	…	2/325	0.6
Grade 3	2/231	0.9	0	…	2/325	0.6
Hypernatremia	0	…	1/94	1.1	1/325	0.3
Grade 4	0	…	1/94	1.1	1/325	0.3
Hypokalemia	1/231	0.4	0	…	1/325	0.3
Grade 3	1/231	0.4	0	…	1/325	0.3
Hyponatremia	5/231	2.2	0	…	5/325	1.5
Grade 3	5/231	2.2	0	…	5/325	1.5
Hematology						
Coagulation: activated partial thromboplastin time prolonged	1/230	0.4	1/94	1.1	2/324	0.6
Grade 3	1/230	0.4	1/94	1.1	2/324	0.6
Differential: lymphocyte count decreased	1/231	0.4	1/94	1.1	2/325	0.6
Grade 3	0	…	1/94	1.1	1/325	0.3
Grade 4	1/231	0.4	0		1/325	0.3
Differential: neutrophil count decreased	5/231	2.2	1/94	1.1	6/325	1.8
Grade 3	4/231	1.7	1/94	1.1	5/325	1.5
Grade 4	1/231	0.4	0	…	1/325	0.3

CTCAE=Common Terminology Criteria for Adverse Events; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; GGT=gamma-glutamyl transferase; ISS=integrated summary of safety; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ≥1 event; Na=number of participants in the analysis set and pooling group with data for the parameter; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: Unless specified, all clinical laboratory abnormalities were treatment-emergent. The worst-case abnormality is defined as the highest/lowest abnormal post-baseline value that was not present at baseline, considering all post-baseline assessments (including unscheduled assessments).

Vital Signs and Physical Examination

ARGX-113-1802 (Overall Population)

In ARGX-113-1802, there were no clinically meaningful changes over time in mean vital sign (heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), or body temperature) actual values or mean changes from baseline.

In Stage B, treatment-emergent shifts in SBP from a normal baseline value to an abnormally high value occurred more frequently (≥5% difference between the treatment arms) in the efgartigimod PH20 SC arm than in the placebo arm (13 [11.7%] and 7 [6.4%], respectively). Treatment-emergent shifts in DBP from a normal baseline value to an abnormally high value occurred in 14 (12.6%) and 14 (12.8%) participants in the efgartigimod PH20 SC and placebo arms, respectively.

ARGX-113-1902

In ARGX-113-1902, there were no clinically meaningful changes from baseline in heart rate or body temperature.

No notable difference (≥5% difference between the groups) was observed for shifts in SBP and DBP between the 1802 Stage B EFG PH20 SC group (8 [8.2%] and 9 [9.3%], respectively) and 1802 Stage B PBO group (6 [6.1%] and 10 [10.1%] participants, respectively).

Pooled Safety Data Set

There were no clinically meaningful changes in heart rate or body temperature. Treatment-emergent shifts to high SBP and DBP were reported for 30 (12.9%) and 48 (20.7%) participants, respectively. These shifts were not considered clinically meaningful.

In the total group, AEs of hypertension and BP increased were reported for 6 (1.8%) and 3 (0.9%) participants, respectively. None of these AEs were serious.

Electrocardiogram

Studies ARGX-113-1802 and ARGX-113-1902

Worst-case electrocardiogram (ECG) parameter abnormalities are presented for ARGX-113-1802 and ARGX-113-1902 in Table 61.

ARGX-113-1802 (Overall Population)

In ARGX-113-1802, there were no clinically meaningful changes over time in mean ECG parameter actual values or mean changes from baseline.

During the study, none of the participants had QTcF values of >500 ms. An increase in QTcF from baseline of >60 ms occurred in 1 participant in the efgartigimod PH20 SC arm during Stage B.

In Stage B, an abnormally high (>220 ms) PR interval occurred more frequently (difference of ≥5% of the participants) in the efgartigimod PH20 SC arm than the placebo arm (6 [5.6%] and 0 participants, respectively). The frequency of other abnormalities was comparable (<5% difference between the treatment arms) between the efgartigimod PH20 SC arm and placebo arm.

ARGX-113-1902

In ARGX-113-1902, none of the participants had QTcF values of >500 ms. An increase in QTcF from baseline of >60 ms was observed in 1 (1.1%) participant in the 1802 Stage B PBO group.

Table 61: Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902: Worst-Case ECG Parameter Abnormalities (Safety Analysis Set)

	Study ARGX-113-1802						Study ARGX-113-1902	
	Stage A		Stage B					
	Efgartigimod PH20 SC (N=322)		Efgartigimod PH20 SC (N=111)		Placebo (N=110)		Total (N=228)	
	n/Na	%	n/Na	%	n/Na	%	n/Na	%
Heart rate (bpm)								
Low (<40)	0	…	0	…	0	…	0	…
High (>100)	2/302	0.7	4/110	3.6	3/106	2.8	2/223	0.9
PR interval (ms)								
Low (<120)	1/296	0.3	4/107	3.7	3/105	2.9	3/218	1.4
High (>220)	3/296	1.0	6/107	5.6	0	…	3/218	1.4
QRS duration (ms)								
High (>120)	1/302	0.3	1/110	0.9	1/106	0.9	1/223	0.4
QTcF interval (ms)								
>450 to 480	3/302	1.0	4/110	3.6	4/106	3.8	5/223	2.2
>480 to 500	0	…	3/110	2.7	0	…	2/223	0.9
> 500	0	…	0	…	0	…	0	…
Change from baseline >30 to 60	7/302	2.3	2/109	1.8	6/100	6.0	11/215	5.1
Change from baseline >60	0	…	1/109	0.9	0	…	1/215	0.5

bpm=beats per minute; CSR=clinical study report; ECG=electrocardiogram; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; ms=milliseconds; N=number of participants in the safety analysis set per treatment group; n=number of participants who reported ≥1 event; Na=number of participants in the analysis set and treatment group with data for the parameter; PR=PR interval; QRS=duration of ventricular depolarization; QTcF=Fridericia's corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: Unless specified, all ECG abnormalities were treatment-emergent. The most severe abnormality is defined as the highest and/or the lowest abnormal post-baseline value that was not present at baseline, considering all post-baseline assessments (including unscheduled assessments).

Pooled Safety Data Set

Worst-case ECG parameter abnormalities are presented for the pooled safety data set in Table 62.

Efgartigimod PH20 SC had no clinically meaningful impact on ECG parameters.

None of the participants had QTcF values of >500 ms and 1 (0.3%) participant had an increase in QTcF from baseline of >60 ms.

Table 62: SC Pooling Block: Worst-Case ECG Parameter Abnormalities (Safety Analysis Set)

	PG1: Efgartigimod PH20 SC (only) (N=235)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94)		PG3: Total pooled group (N=329)	
	n/Na	%	n/Na	%	n/Na	%
Heart rate (bpm)						
Low (<40)	0	…	0	…	0	…
High (>100)	5/219	2.3	4/94	4.3	9/313	2.9

PR (ms)						
Low (<120)	4/216	1.9	3/92	3.3	7/308	2.3
High (>220)	9/216	4.2	0		9/308	2.9
QRS duration (ms)						
High (>120)	2/219	0.9	1/94	1.1	3/313	1.0
QTcF (ms)						
>450 to 480	9/219	4.1	2/94	2.1	11/313	3.5
>480 to 500	2/219	0.9	2/94	2.1	4/313	1.3
>500	0	…	0	…	0	…
Change from baseline >30 to 60	12/219	5.5	9/94	9.6	21/313	6.7
Change from baseline >60	1/219	0.5	0	…	1/313	0.3

bpm=beats per minute; ECG=electrocardiogram; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; ISS=integrated summary of safety; ms=milliseconds; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; Na=number of participants in the analysis set and pooling group with data for the parameter; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PR=PR interval; PYFU=participant years of follow-up; QRS=duration of ventricular depolarization; QTcF=Fridericia's corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: Unless specified, all ECG abnormalities were treatment-emergent. The most severe treatment-emergent abnormality is defined as the highest and/or the lowest abnormal post-baseline value that was not present at baseline, considering all post-baseline assessments (including unscheduled assessments).

Suicidality

At each visit during the studies, participants were asked to respond to the following question (Patient Health Questionnaire-9): "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?" Response options were limited to the following: "not at all," "several days," "more than half the days," or "nearly every day."

ARGX-113-1802 (Overall Population)

Most participants (304 [94.7%]) had no suicidal thoughts (responded "not at all") during Stage A, including 6 (1.9%) participants who had suicidal thoughts for several days over the last 2 weeks at Stage A baseline. Overall, 7 (2.2%) participants had a worsening of suicidal thoughts from Stage A baseline at least once during Stage A.

Most participants (108 [97.3%] and 103 [94.5%] participants in the efgartigimod PH20 SC and placebo arm, respectively) had no suicidal thoughts (responded "not at all") during Stage B. Overall, 2 (1.8%) participants in the efgartigimod PH20 SC and 6 (5.5%) participants in the placebo arm had a worsening of suicidal thoughts from Stage B baseline at least once during Stage B.

ARGX-113-1902

Most participants (215 [97.7%]) had no suicidal thoughts (responded "not at all").

One (0.5%) participant in the 1802 Stage B PBO group who did not have suicidal thoughts over the last 2 weeks at baseline had suicidal thoughts more than half of the days over 2 weeks at least once during the study.

There was no pooled analysis of the suicidality assessment.

Safety in special populations

Age

AEs that occurred more frequently (≥10 % difference) in participants of either subgroup are summarized by category and by MedDRA SOC and PT in table 63.

A review of demographic and baseline disease characteristics by age showed that most participants (253 [76.9%]) were 18 to <65 years of age and, within this age group, were male (158 [62.5%] participants). Overall, 76 (23.1%) participants were ≥65 years of age. The majority of the participants within this age group were male (54 [71.1%] participants).

In the 18 to <65 years category, the median (min, max) time since CIDP diagnosis at ARGX-113-1802 Stage A baseline was 2.93 (0.0, 46.1) years, and was similar (2.75 [0.0, 30.8] years) to that in the ≥65 years category. Prior CIDP therapy at the time of screening included IVIg or SCIg for 133 (52.6%) participants 18 to <65 years and 35 (46.1%) participants ≥65 years of age, and corticosteroids for 49 (19.4%) and 16 (21.1%) participants 18 to <65 and ≥65 years of age, respectively. In total, 71 (28.1%) and 25 (32.9%) participants to <65 and ≥65 years of age, respectively, were treatment naïve at the time of screening.

The median (min, max) treatment duration was 21.0 (1, 152) and 15.0 (1, 142) weeks in the 18 to <65 years and ≥65 years category, respectively.

Table 63: Summary of AEs by Category and by MedDRA SOC and PT Occurring More Frequently (≥ 10% Difference) in Either Age Subgroup

	18 to <65 years (N=253) n (%)	**≥65 years (N=76) n (%)**
AEs by category		
≥1 Treatment-related AE	126 (49.8)	22 (28.9)
≥1 Procedure-related AE	41 (16.2)	4 (5.3)
≥1 AESI	111 (43.9)	23 (30.3)
≥1 Injection-site reaction	71 (28.1)	13 (17.1)
≥1 Injection-related reaction	75 (29.6)	10 (13.2)
AEs by MedDRA SOC and PT		
General disorders and administration site conditions	92 (36.4)	17 (22.4)
Infections and infestations	111 (43.9)	23 (30.3)
Nervous system disorders	63 (24.9)	11 (14.5)

AE=adverse event; AESI=adverse event of special interest; ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per subgroup; n=number of participants who reported ≥1 event; PT=Preferred Term; SOC=System Organ Class

Sex at Birth

In the total pooled group, 212 (64.4%) participants were male and 117 (35.6%) were female. The majority of both male and female participants were 18 to <65 years old (158 [74.5%] participants and 95 [81.2%] participants, respectively). In the total pooled group, 54 (25.5%) male and 22 (18.8%)

female participants were ≥65 years. The mean (SD) BMI was similar for male and female participants (26.84 [4.827] and 26.72 [6.184] kg/m2, respectively).

The median (min, max) time since CIDP diagnosis at ARGX-113-1802 Stage A baseline was 2.63 (0.0, 30.8) years for male participants and 3.24 (0.0, 46.1) years for female participants. Prior CIDP therapy at the time of screening was IVIg and SCIg for 103 (48.6%) male participants and 65 (55.6%) female participants and corticosteroids for 43 (20.3%) male and 22 (18.8%) female participants. In total, 66 (31.1%) and 30 (25.6%) male and female participants, respectively, were treatment naïve at time of screening.

The median (min, max) treatment duration was 18.0 (1, 146) and 20.0 (1, 152) weeks for the male and female participants, respectively.

Overall, 171 (80.7%) male participants and 97 (82.9%) female participants had ≥1 AE. A higher percentage (≥10% difference) of female participants had ≥1 injection-site reaction compared with male participants (39 [33.3%] vs 45 [21.2%], respectively). There were no other differences of ≥10% between the subgroups for AE by category, SOC, or PT.

All 3 SAEs leading to death that started ≤60 days after the last efgartigimod PH20 SC dose occurred in male participants.

Race

AEs that occurred more frequently (≥10 % difference) in participants of either subgroup are summarized by category and by MedDRA SOC and PT in Table 64.

The majority of the participants were White (216 [67.9%] participants). Overall, 91 (28.6%) participants were Asian, 4 (1.3%) were Black or African American, and 7 (2.2%) were categorized as race "Other." Because the number of Black or African American participants or participants of other races was limited (<15 participants), these subgroups are excluded from the below comparison.

The majority of the White and Asian participants were 18 to <65 years (159 [73.6%] and 76 [83.5%] participants, respectively) and male (139 [64.4%] and 61 [67.0%] participants, respectively). In the total pooled group, 57 (26.4%) of the White and 15 (16.5%) of the Asian participants were ≥65 years. The mean (SD) BMI was 27.66 [5.261] kg/m2 for White and 24.05 [3.674] kg/m2 for Asian participants.

The median (min, max) time since CIDP diagnosis at ARGX-113-1802 Stage A baseline was 3.04 (0.0, 46.1) years for White participants and 1.98 (0.0, 28.8) years for Asian participants. Prior CIDP therapy at the time of screening was IVIg and SCIg for 115 (53.2%) White participants and 34 (37.4%) Asian participants and corticosteroids for 37 (17.1%) and 26 (28.6%) White and Asian participants, respectively. In total, 64 (29.6%) and 31 (34.1%) White and Asian participants, respectively, were treatment naïve at the time of screening.

The median (min, max) treatment duration was 23.0 (1, 152) and 18.0 (1, 104) weeks for White and Asian participants, respectively.

Overall, 169 (78.2%) White participants and 79 (86.8%) Asian participants had ≥1 AE. Differences between the race subgroups may reflect the variation between regions in the occurrence of AEs, in general, and by category.

Table 64: Summary of AEs by Category and by MedDRA SOC and PT Occurring More Frequently (⩾ 10% Difference) in Either Race Subgroup

	White (N=169) n (%)	Asian (N=79) n (%)
AEs by category		
≥1 Treatment-related AE	77 (35.6)	60 (65.9)
≥1 AE for which the IMP was interrupted	36 (16.7)	27 (29.7)
≥1 AESI	78 (36.1)	47 (51.6)
AEs by MedDRA SOC and PT		
Gastrointestinal disorders	21 (9.7)	19 (20.9)
Infections and infestations	78 (36.1)	47 (51.6)
COVID-19	30 (13.9)	25 (27.5)
Upper respiratory tract infection	13 (6.0)	17 (18.7)
Investigations	37 (17.1)	31 (34.1)

AE=adverse event; AESI=adverse event of special interest; ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per subgroup; n=number of participants who reported ⩾1 event; PT=Preferred Term; SOC=System Organ Class

Body Weight and BMI

Body weight at screening ranged from 37.7 to 136.5 kg in the total pooled group with a mean (SD) body weight of 78.89 (18.753) kg. Overall, 133 (40.7%) participants had a baseline body weight of 50 to <75 kg, 131 (40.1%) participants had a baseline body weight of 75 to <100 kg, and 48 (14.7%) participants had a baseline body weight of 100 to <125 kg. Because the number of participants with a baseline body weight <50 kg (12 [3.6%]) participants and a baseline body weight ≥125 kg (3 [0.9%]) was limited (<15 participants), these subgroups were excluded from the evaluation of safety by body weight category.

Approximately half of the participants in the body weight 50 to <75 kg (66 [49.6%]) category were female. In the 75 to <100 kg and 100 to <125 kg body weight categories, 98 (74.8%) and 40 (83.3%) participants, respectively, were male.

Key baseline disease characteristics by body weight category are summarized in Table 65.

Table 65: Key Baseline Disease Characteristics by Body Weight Category

	50 to <75 kg (N=133)	75 to <100 kg (N=131)	100 to <125 kg (N=48)
Time since CIDP diagnosis (years); median (min, max)	2.61 (0.0, 46.1)	3.16 (0.0, 30.8)	2.59 (0.0, 22.9)
Prior CIDP therapy; n(%)			
IVIg or SCIg	63 (47.4)	67 (51.1)	29 (60.4)
Corticosteroids	29 (21.8)	24 (18.3)	8 (16.7)
Treatment naïve	41 (30.8)	40 (30.5)	11 (22.9)

CIDP=chronic inflammatory demyelinating polyneuropathy; ISS=integrated summary of safety; IVIg=intravenous immunoglobulin; max=maximum; min=minimum; n=number of participants for whom the observation was reported; SCIg=subcutaneous immunoglobulin

The median (min, max) treatment duration was longer in participants with body weight 75 to <100 kg and 100 to <125 kg (24.0 [1, 146] and 37.5 [1, 143] weeks, respectively) compared with participants with body weight 50 to <75 kg (15.0 [1, 152] weeks).

There was a trend toward an increasing percentage of participants with ≥1 AE with increasing body weight: 104 (78.2%), 108 (82.4%), and 44 (91.7%) participants in the 50 to <75 kg, 75 to <100 kg, and 100 to <125 kg categories, respectively. AEs that occurred more frequently (≥10% difference) in participants of either subgroup are summarized by category and by MedDRA SOC and PT in Table 66.

Table 66: Summary of AEs by Category and by MedDRA SOC and PT Occurring More Frequently (⩾ 10% Difference) in Any of the Body Weight Category Subgroups

	50 to <75 kg (N=133) n (%)	**75 to <100 kg (N=131) n (%)**	**100 to <125 kg (N=48) n (%)**
AEs by category			
≥1 AE	104 (78.2)	108 (82.4)	44 (91.7)
≥1 SAE	20 (15.0)	18 (13.7)	12 (25.0)
AEs by MedDRA SOC and PT			
Eye disorders	4 (3.0)	3 (2.3)	6 (12.5)
General disorders and administration site conditions	43 (32.3)	38 (29.0)	22 (45.8)
Injury, poisoning and procedural complications	12 (9.0)	17 (13.0)	12 (25.0)
Fall	5 (3.8)	3 (2.3)	8 (16.7)
Respiratory, thoracic and mediastinal disorders	10 (7.5)	8 (6.1)	9 (18.8)

AE=adverse event; ISS=integrated summary of safety; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per subgroup; n=number of participants who reported ⩾1 event; PT=Preferred Term; SOC=System Organ Class

BMI at screening ranged from 16.4 kg/m² to 47.7 kg/m² in the total pooled group with a mean (SD) BMI of 26.80 (5.340) kg/m². Overall, 135 (41.4%) of the participants had a normal weight (BMI 18.5 to <25 kg/m²) at baseline, 104 (31.9%) participants had overweight (BMI 25 to <30 kg/m²), and 80 (24.5%) were obese (BMI ≥30 kg/m²). The number of participants with underweight (BMI <18.5 kg/m2; 7 [2.1%]) was limited and was excluded from the comparison.

Overall, 107 (79.3%) participants with normal weight, 88 (84.6%) participants with overweight, and 67 (83.8%) participants who were obese had ≥1 AE. Except for ≥1 SAE (20 [14.8%], 11 [10.6%], and 20 [25.0%], in participants with normal weight, overweight, and obesity, respectively), AEs grade ≥3 (24 [17.8%], 15 [14.4%], and 20 [25.0%], respectively), and AEs leading to IMP discontinuation (13 [9.6%], 7 [6.7%], and 14 [17.5%], respectively), there were no differences of ≥10% between the subgroups for AEs by category, SOC, or PT.

Hepatic Impairment

There have been no clinical studies of efgartigimod in participants with hepatic impairment, and the safety of efgartigimod in this population is unknown.

Renal Impairment

There have been no completed clinical studies of efgartigimod in participants with renal impairment.

There were insufficient data to evaluate the effect of moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m2) and severe renal impairment (eGFR <30 mL/min/1.73 m²) on the safety of efgartigimod PH20 SC in participants with CIDP in ARGX-113-1802.

In studies in participants with gMG, safety data were analyzed by baseline renal function based on eGFR value. A review of the clinical safety data showed that mild renal impairment did not impact the safety profile of efgartigimod PH20 SC.

Immunogenicity

Incidence and Prevalence of ADA Against Efgartigimod (Stage A)

The participant classification, incidence, and prevalence of ADA against efgartigimod in Stage A are summarized in Table 67.

Table 67: Participant Classification, Incidence, and Prevalence of ADA Against Efgartigimod in Study ARGX-113-1802 (IMM-A Analysis Set)

	Efgartigimod PH20 SC (N=322) n (%)
Overall[a]	
ADA-evaluable participants	317 (98.4)
ADA-unevaluable participants	5 (1.6)
Baseline ADA sample status[b]	
ADA negative	304 (95.9)
ADA positive	13 (4.1)
ADA participant classification[b]	
ADA negative	297 (93.7)
ADA negative	285 (89.9)
Treatment-unaffected ADA	12 (3.8)
ADA positive	20 (6.3)
Treatment-induced ADA	19 (6.0)
Treatment-boosted ADA	1 (0.3)
Incidence/prevalence[b]	
ADA incidence	20 (6.3)
ADA prevalence	32 (10.1)

ADA=antidrug antibody(ies); efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-A=Stage A immunogenicity analysis set; N=number of participants in the IMM-A analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-A includes participants from the Stage A safety analysis set for whom at least 1 ADA sample during Stage A is available. ADA incidence was defined as the total number of participants with treatment boosted or treatment-induced ADA. ADA prevalence was defined as the total number of participants with treatment-unaffected, treatment-boosted, or treatment-induced ADA. Stage A baseline was used to determine the ADA against efgartigimod participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-A analysis set.
b The denominator for the percent calculations was the number of ADA-evaluable participants in the IMM-A analysis set.

Incidence and Prevalence of ADA Against Efgartigimod (Stage B)

The participant classification, incidence, and prevalence of ADA against efgartigimod in the treatment arms in Stage B are summarized in Table 68.

In the efgartigimod PH20 SC arm, the incidence and prevalence of ADA against efgartigimod were 1.8% and 2.7%, respectively. In the placebo arm, the incidence and prevalence were both 58.7%. ADA against efgartigimod in the placebo arm of Stage B may be due to pre-existing antibodies from Stage A baseline or antibodies induced during treatment with efgartigimod PH20 SC in Stage A. These antibodies were not detected during the administration of efgartigimod in Stage A when total IgG levels were low (including ADA); however, ADA were detected in the placebo arm of Stage B after treatment withdrawal and a subsequent increase in total IgG (including ADA) when efgartigimod was no longer detected.

Table 68: Participant Classification, Incidence, and Prevalence of ADA Against Efgartigimod in Study ARGX-113-1802 (IMM-B Analysis Set)

	EFG PH20 SC (N=111) n (%)	**PBO PH20 SC (N=110) n (%)**	**Total (N=221) n (%)**
Overall[a]			
ADA-evaluable participants	111 (100)	109 (99.1)	220 (99.5)
ADA-unevaluable participants	0	1 (0.9)	1 (0.5)
Baseline ADA sample status[b]			
ADA negative	110 (99.1)	108 (99.1)	218 (99.1)
ADA positive	1 (0.9)	1 (0.9)	2 (0.9)
ADA participant classification[b]			
ADA negative	109 (98.2)	45 (41.3)	154 (70.0)
ADA negative	108 (97.3)	45 (41.3)	153 (69.5)
Treatment-unaffected ADA	1 (0.9)	0	1 (0.5)
ADA positive	2 (1.8)	64 (58.7)	66 (30.0)
Treatment-induced ADA	2 (1.8)	63 (57.8)	65 (29.5)
Treatment-boosted ADA	0	1 (0.9)	1 (0.5)
Incidence/prevalence[b]			
ADA incidence	2 (1.8)	64 (58.7)	66 (30.0)
ADA prevalence	3 (2.7)	64 (58.7)	67 (30.5)

ADA=antidrug antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-B=Stage B immunogenicity analysis set; N=number of participants in the IMM-B analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-B includes participants from the Stage B safety analysis set for whom at least 1 ADA sample during Stage B is available. ADA incidence was defined as the total number of participants with treatment-boosted or treatment-induced ADA. ADA prevalence was defined as the total number of participants with treatment-unaffected, treatment-boosted, or treatment-induced ADA. Stage B baseline was used to determine the ADA against efgartigimod participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-B analysis set.
b The denominator for the percent calculations was the number of ADA-evaluable participants in the IMM-B analysis set.

Incidence and Prevalence of ADA Against Efgartigimod (Stages A and B)

The participant classification, incidence, and prevalence of ADA against efgartigimod are summarized in Table 69 for participants who received efgartigimod PH20 SC in both Stage A and Stage B.

Table 69: Participant Classification, Incidence, and Prevalence of ADA Against Efgartigimod in Study ARGX-113-1802 (IMM-AB Analysis Set)

	EFG PH20 SC (N=111) n (%)
Overall[a]	
ADA-evaluable participants	111 (100)
ADA-unevaluable participants	0
Baseline ADA sample status[b]	
ADA negative	107 (96.4)
ADA positive	4 (3.6)
ADA participant classifications[b]	
ADA negative	108 (97.3)
ADA negative	104 (93.7)
Treatment-unaffected ADA	4 (3.6)
ADA positive	3 (2.7)
Treatment-induced ADA	3 (2.7)
Treatment-boosted ADA	0
Incidence/prevalence[b]	
ADA incidence	3 (2.7)
ADA prevalence	7 (6.3)

ADA=antidrug antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-AB=Stages A and B combined immunogenicity analysis set; N=number of participants in the IMM-AB analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-AB includes participants who received at least (part of) 1 dose of efgartigimod PH20 SC in Stage B, for whom at least 1 ADA sample during Stage A or Stage B is available. ADA incidence was defined as the total number of participants with treatment-boosted or treatment-induced ADA. ADA prevalence was defined as the total number of participants with treatment-unaffected, treatment-boosted, or treatment-induced ADA. Stage A baseline was used to determine the ADA against efgartigimod participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-AB analysis set.
b The denominator for the percent calculations was the number of ADA-evaluable participants in the IMM-AB analysis set.

Incidence and Prevalence of NAb Against Efgartigimod (Stage A)

The participant classification, incidence, and prevalence of NAb against efgartigimod in Stage A are summarized in Table 70.

Table 70: Participant Classification, Incidence, and Prevalence of NAb Against Efgartigimod in Study ARGX-113-1802 (IMM-A Analysis Set)

	Efgartigimod PH20 SC (N=322) n (%)
Overall[a]	
NAb-evaluable participants	317 (98.4)
NAb-unevaluable participants	5 (1.6)
Baseline NAb sample status[b]	
NAb negative	317 (100)
NAb positive	0
NAb participant classification[b]	
NAb negative	316 (99.7)
Baseline negative – postbaseline negative	316 (99.7)
Baseline positive – postbaseline negative	0
NAb positive	1 (0.3)
Baseline negative – postbaseline positive	1 (0.3)
Baseline positive – postbaseline positive	0
Incidence/prevalence[b]	
NAb incidence	1 (0.3)
NAb prevalence	1 (0.3)

efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-A=Stage A immunogenicity analysis set; N=number of participants in the IMM-A analysis set; NAb=neutralizing antibody(ies); n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-A includes participants from the Stage A safety analysis set for whom at least 1 ADA sample during Stage A is available. NAb incidence was defined as the total number of participants with baseline negative – postbaseline positive and baseline positive – postbaseline positive. NAb prevalence was defined as the total number of participants with baseline positive – postbaseline positive, baseline negative – postbaseline positive, and baseline positive – postbaseline negative. Stage A baseline was used to determine the NAb against efgartigimod participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-A analysis set.
b The denominator for the percent calculations was the number of NAb-evaluable participants in the IMM-A analysis set.

Incidence and Prevalence of NAb Against Efgartigimod (Stage B)

The participant classification, incidence, and prevalence of NAb against efgartigimod in the treatment arms in Stage B are summarized in table 71.

Table 71: Participant Classification, Incidence, and Prevalence of NAb Against Efgartigimod in Study ARGX-113-1802 (IMM-B Analysis Set)

	EFG PH20 SC (N=111) n (%)	PBO PH20 SC (N=110) n (%)	Total (N=221) n (%)
Overall[a]			
NAb-evaluable participants	111 (100)	109 (99.1)	220 (99.5)
NAb-unevaluable participants	0	1 (0.9)	1 (0.5)
Baseline NAb sample status[b]			
NAb negative	111 (100)	109 (100)	220 (100)
NAb positive	0	0	0
NAb participant classification[b]			
NAb negative	111 (100)	96 (88.1)	207 (94.1)
Baseline negative - postbaseline negative	111 (100)	96 (88.1)	207 (94.1)
Baseline positive - postbaseline negative	0	0	0
NAb positive	0	13 (11.9)	13 (5.9)
Baseline negative - postbaseline positive	0	13 (11.9)	13 (5.9)
Baseline positive - postbaseline positive	0	0	0
Incidence/prevalence[b]			
NAb incidence	0	13 (11.9)	13 (5.9)
NAb prevalence	0	13 (11.9)	13 (5.9)

EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-B=Stage B immunogenicity analysis set; N=number of participants per treatment group in the IMM-B analysis set; NAb=neutralizing antibodies; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-B includes participants from the Stage B safety analysis set for whom at least 1 ADA sample during Stage B is available. NAb incidence was defined as the percentage of participants with a positive postbaseline sample, including participant classes "NAb baseline negative–postbaseline positive" and "NAb baseline positive– postbaseline positive." NAb prevalence was defined as the percentage of participants with any positive NAb sample, including baseline. This includes all participants of participant classes "NAb baseline negative–postbaseline positive," "NAb baseline positive–postbaseline negative," and "NAb baseline positive–postbaseline positive." Stage B baseline was used to determine the ADA against efgartigimod participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-B analysis set.
b The denominator for the percent calculations was the number of NAb-evaluable participants in the IMM-B analysis set.

Incidence and Prevalence of NAb Against Efgartigimod (Stages A and B)

NAb status was evaluable in 111 (100%) participants.

No positive NAb samples were reported at study baseline. Across Stages A and B, the incidence and prevalence of NAb against efgartigimod were both 0%.

Impact of Pre-Ab, ADA, and NAb Against Efgartigimod on Safety

The impact of ADA against efgartigimod on safety was evaluated by comparing the incidences of AEs and SAEs across the antibody categories in Stages A and B. All AEs and SAEs were treatment-emergent unless specified.

In Stages A and B, the occurrence of AEs and SAEs was similar between ADA-positive and ADA-negative participants (Table 72 and Table 73, respectively).

Table 72: Percentage of Participants With Any AE or SAE by Participant Classification of ADA Against Efgartigimod (Stage A Safety Analysis Set)

Participant classification	Efgartigimod PH20 SC % (n/N)	
	AE	SAE
Total	63.4 (204/322)	6.5 (21/322)
ADA negative	61.8 (176/285)	5.6 (16/285)
Treatment-unaffected ADA	75.0 (9/12)	8.3 (1/12)
Treatment-induced ADA	73.7 (14/19)	5.3 (1/19)
Treatment-boosted ADA	100.0 (1/1)	100.0 (1/1)
ADA unevaluable	80.0 (4/5)	40.0 (2/5)

ADA=antidrug antibody(ies); AE=adverse event(s); efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group in the Stage A safety analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event(s); SC=subcutaneous(ly)

Table 73: Percentage of Participants With Any AE or SAE by Participant Classification of ADA Against Efgartigimod (Stage B Safety Analysis Set)

Participant classification	AE		SAE	
	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)
Total	64.0 (71/111)	56.4 (62/110)	5.4 (6/111)	5.5 (6/110)
ADA negative	63.9 (69/108)	48.9 (22/45)	5.6 (6/108)	6.7 (3/45)
Treatment-unaffected ADA	100.0 (1/1)	0	0.0 (0/1)	0
Treatment-induced ADA	50.0 (1/2)	61.9 (39/63)	0.0 (0/2)	4.8 (3/63)
Treatment-boosted ADA	0	100.0 (1/1)	0	0.0 (0/1)
ADA unevaluable	0	0.0 (0/1)	0	0.0 (0/1)

ADA=antidrug antibody(ies); AE=adverse event(s); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group and treatment group in the Stage B safety analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event(s); SC=subcutaneously

The impact of ADA against efgartigimod was further evaluated by comparing the incidences of injection-related reactions and AEs of Injection site reactions across the ADA categories in Stage A and Stage B.

In Stages A and B, the occurrence of injection-related reactions and AEs of Injection site reactions was similar between ADA-positive and ADA-negative participants (Table 74 and Table 75, respectively).

No anaphylactic reactions were reported.

Table 74: Percentage of Participants With Any Injection-Related Reaction or AEs of Injection Site Reactions by Participant Classification of ADA Against Efgartigimod (Stage A Safety Analysis Set)

Participant classification	EFG PH20 SC % (n/N)	
	Injection-related reaction	Injection site reaction
Total	19.9 (64/322)	19.3 (62/322)
ADA negative	20.4 (58/285)	18.9 (54/285)
Treatment-unaffected ADA	16.7 (2/12)	25.0 (3/12)
Treatment-induced ADA	21.1 (4/19)	26.3 (5/19)
Treatment-boosted ADA	0.0 (0/1)	0.0 (0/1)
ADA unevaluable	0.0 (0/5)	0.0 (0/5)

ADA=antidrug antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group in the Stage A safety analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Table 75: Percentage of Participants With Any Injection-Related Reaction or AE of Injection Site Reactions by Participant Classification of ADA Against Efgartigimod (Stage B Safety Analysis Set)

Participant classification	Injection-related reaction		Injection site reaction	
	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)
Total	9.9 (11/111)	5.5 (6/110)	14.4 (16/111)	6.4 (7/110)
ADA negative	9.3 (10/108)	6.7 (3/45)	13.9 (15/108)	6.7 (3/45)
Treatment-unaffected ADA	100.0 (1/1)	0	100.0 (1/1)	0
Treatment-induced ADA	0.0 (0/2)	4.8 (3/63)	0.0 (0/2)	6.3 (4/63)
Treatment-boosted ADA	0	0.0 (0/1)	0	0.0 (0/1)
ADA unevaluable	0	0.0 (0/1)	0	0.0 (0/1)

ADA=antidrug antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group and treatment group in the Stage B safety analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Incidence and Prevalence of Antibodies Against rHuPH20 (Stage A)

The participant classification, incidence, and prevalence of antibodies against rHuPH20 in Stage A are summarized in table 76.

Table 76: Participant Classification, Incidence, and Prevalence of Antibodies Against rHuPH20 in Study ARGX-113-1802 (IMM-A Analysis Set)

	EFG PH20 SC (N=322) n (%)
Overall[a]	
rHuPH20 Ab-evaluable participants	316 (98.1)
rHuPH20 Ab-unevaluable participants	6 (1.9)

Baseline rHuPH20 Ab sample status[b]	
rHuPH20 Ab negative	241 (76.3)
rHuPH20 Ab positive	75 (23.7)
rHuPH20 Ab participant classification[b]	
rHuPH20 Ab negative	271 (85.8)
rHuPH20 Ab negative	213 (67.4)
Treatment-unaffected rHuPH20 Ab	58 (18.4)
rHuPH20 Ab positive	45 (14.2)
Treatment-induced rHuPH20 Ab	28 (8.9)
Treatment-boosted rHuPH20 Ab	17 (5.4)
Incidence/prevalence[b]	
rHuPH20 Ab incidence	45 (14.2)
rHuPH20 Ab prevalence	103 (32.6)

Ab=antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-A=Stage A immunogenicity analysis set; N=number of participants per treatment group in the IMM-A analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-A includes participants from the Stage A safety analysis set for whom at least 1 immunogenicity sample during Stage A is available. Incidence was defined as the total number of participants with treatment-boosted or treatment-induced antibodies against rHuPH20. Prevalence was defined as the total number of participants with treatment-unaffected, treatment-boosted, or treatment-induced antibodies against rHuPH20. Stage A baseline was used to determine the antibodies against rHuPH20 participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-A analysis set.
b The denominator for the percent calculations was the number of rHuPH20 Ab-evaluable participants in the IMMA analysis set.

Incidence and Prevalence of Antibodies Against rHuPH20 (Stage B)

The participant classification, incidence, and prevalence of antibodies against rHuPH20 in the treatment arms in Stage B are summarized in Table 77.

Table 77: Participant Classification, Incidence, and Prevalence of Antibodies Against rHuPH20 in Study ARGX-113-1802 (IMM-B Analysis Set)

	EFG PH20 SC (N=111) n (%)	**PBO PH20 SC (N=110) n (%)**	**Total (N=221) n (%)**
Overall[a]			
rHuPH20 Ab-evaluable participants	111 (100)	109 (99.1)	220 (99.5)
rHuPH20 Ab-unevaluable participants	0	1 (0.9)	1 (0.5)
Baseline rHuPH20 Ab sample status[b]			
rHuPH20 Ab negative	102 (91.9)	99 (90.8)	201 (91.4)
rHuPH20 Ab positive	9 (8.1)	10 (9.2)	19 (8.6)
rHuPH20 Ab participant classification[b]			
rHuPH20 Ab negative	59 (53.2)	77 (70.6)	136 (61.8)
rHuPH20 Ab negative	59 (53.2)	76 (69.7)	135 (61.4)
Treatment-unaffected rHuPH20 Ab	0	1 (0.9)	1 (0.5)
rHuPH20 Ab positive	52 (46.8)	32 (29.4)	84 (38.2)
Treatment-induced rHuPH20 Ab	43 (38.7)	23 (21.1)	66 (30.0)
Treatment-boosted rHuPH20 Ab	9 (8.1)	9 (8.3)	18 (8.2)

Incidence/prevalence[b]			
rHuPH20 Ab incidence	52 (46.8)	32 (29.4)	84 (38.2)
rHuPH20 Ab prevalence	52 (46.8)	33 (30.3)	85 (38.6)

Ab=antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMM-B=Stage B immunogenicity analysis set; N=number of participants per treatment group in the IMM-B analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-B includes participants from the Stage B safety analysis set for whom at least 1 immunogenicity sample during Stage B is available. The incidence of antibodies against rHuPH20 was defined as the total number of participants with treatment-boosted or treatment-induced antibodies against rHuPH20. The prevalence of antibodies against rHuPH20 was defined as the total number of participants with treatment unaffected, treatment-boosted, or treatment-induced antibodies against rHuPH20. Stage B baseline was used
to determine the antibodies against rHuPH20 participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-B analysis set.
b The denominator for the percent calculations was the number of rHuPH20 Ab-evaluable participants in the IMMB analysis set.

Incidence and Prevalence of Antibodies Against rHuPH20 (Stages A and B)

The participant classification, incidence, and prevalence of antibodies against rHuPH20 are summarised across Stage A and Stage B in Table 78 for participants who received efgartigimod PH20 SC.

Table 78: Participant Classification, Incidence, and Prevalence of Antibodies Against rHuPH20 in Study ARGX-113-1802 (IMM-AB Analysis Set)

	EFG PH20 SC (N=111) n (%)
Overall[a]	
rHuPH20 Ab-evaluable participants	111 (100)
rHuPH20 Ab-unevaluable participants	0
Baseline rHuPH20 Ab sample status[b]	
rHuPH20 Ab negative	98 (88.3)
rHuPH20 Ab positive	13 (11.7)
rHuPH20 participant classification	
rHuPH20 Ab negative	63 (56.8)
rHuPH20 Ab negative	57 (51.4)
Treatment-unaffected rHuPH20 Ab	6 (5.4)
rHuPH20 Ab positive	48 (43.2)
Treatment-induced rHuPH20 Ab	41 (36.9)
Treatment-boosted rHuPH20 Ab	7 (6.3)
Incidence/prevalence	
rHuPH20 Ab incidence	48 (43.2)
rHuPH20 prevalence	54 (48.6)

Ab=antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IM-AB=Stages A and B combined immunogenicity analysis set; N=number of participants in the IMM-AB analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Notes: IMM-AB includes participants from the Stages A and B combined safety analysis set for whom at least 1 immunogenicity sample during Stage A or Stage B is available. The incidence of antibodies against rHuPH20 was defined as the total number of participants with treatment-boosted or treatment-induced antibodies against rHuPH20. The prevalence of antibodies against rHuPH20 was defined as the total number of participants with treatment-unaffected, treatment-boosted, or treatment-induced antibodies against rHuPH20. Stage A baseline was used to determine the antibodies against rHuPH20 participant classification.
a The denominator for the percentage calculations was the number of participants in the IMM-AB analysis set.
b The denominator for the percent calculations was the number of rHuPH20 Ab-evaluable participants in the IMMAB analysis set.

Incidence and Prevalence of NAb Against rHuPH20 (Stage A)

rHuPH20 NAb status was evaluable in 316 (98.1%) participants and unevaluable in 6 (1.9%) participants.

No rHuPH20 NAb screen-positive baseline samples were reported at Stage A baseline.

The incidence and prevalence of NAb against rHuPH20 were both 0%.

Incidence and Prevalence of NAb Against rHuPH20 (Stage B)

rHuPH20 NAb status was evaluable in 220 (99.5%) participants and unevaluable in 1 (0.5%) participant.

No rHuPH20 NAb screen-positive baseline samples were reported at Stage B baseline in either the efgartigimod PH20 SC arm or the placebo arm.

The incidence and prevalence of NAb against rHuPH20 were both 4.5% in the efgartigimod PH20 SC arm and were both 1.8% in the placebo arm.

Incidence and Prevalence of NAb Against rHuPH20 (Stages A and B)

rHuPH20 NAb status was evaluable in 111 (100%) participants.

No rHuPH20 NAb screen-positive baseline samples were reported at study baseline.

The incidence and prevalence of NAb against rHuPH20 were both 4.5%.

An additional NAb confirmatory assay was implemented as a post hoc analysis to determine the specificity of the response, since the Nab against rHuPH20 was higher than expected based on clinical experience with rHuPH201 and efgartigimod PH20 SC.

Following the confirmatory analysis in the 3-tiered approach, the incidence and prevalence of NAb against rHuPH20 were 0% in the efgartigimod PH20 SC and placebo arms.

Impact of Pre-Ab, Antibodies, and NAb Against rHuPH20 on Safety

The impact of antibodies against rHuPH20 on safety was evaluated by comparing the incidences of AEs and SAEs across the antibody categories in Stages A and B.

In Stages A and B, the occurrence of AEs was similar between participants who were positive for antibodies against rHuPH20 and those who were negative (Table 79 and Table 80).

Table 79: Percentage of Participants With Any AE or SAE by Participant Classification of Antibodies Against rHuPH20 (Stage A Safety Analysis Set)

Participant classification	EFG PH20 SC % (n/N)	
	AE	SAE
Total	63.4 (204/322)	6.5 (21/322)
Negative for Ab against rHuPH20	58.7 (125/213)	1.9 (4/213)
Treatment-unaffected Ab against rHuPH20	65.5 (38/58)	12.1 (7/58)
Treatment-induced Ab against rHuPH20	75.0 (21/28)	14.3 (4/28)
Treatment-boosted Ab against rHuPH20	88.2 (15/17)	23.5 (4/17)
Unevaluable for Ab against rHuPH20	83.3 (5/6)	33.3 (2/6)

Ab=antibody(ies); AE=adverse event(s); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group in the Stage A safety set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event(s); SC=subcutaneous(ly)

In Stage A, the occurrence of SAEs was numerically higher in participants with treatment-unaffected (12.1%), treatment-induced (14.3%), and treatment-boosted antibodies (23.5%) against rHuPH20 than in rHuPH20 antibody-negative participants (1.9%). The SAEs by PT were Clostridium difficile colitis, COVID-19, COVID-19 [pneumonia], CIDP, and Quadriparesis. However, the antibody titers were low, and there was no temporal association between the SAEs and the formation of antibodies against rHuPH20; therefore, a causal relationship is unlikely. Furthermore, the participants with an SAE of CIDP received Ig as a rescue medication, which may introduce antibodies against rHuPH20 in these participants by passive transfusion and, therefore, influence the rHuPH20 antibody participant classification.

Table 80: Percentage of Participants With Any AE or SAE by Participant Classification of Antibodies Against rHuPH20 in Study ARGX-113-1802 (Stage B Safety Analysis Set)

Participant classification	AE		SAE	
	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)
Total	64.0 (71/111)	56.4 (62/110)	5.4 (6/111)	5.5 (6/110)
Negative for Ab against rHuPH20	64.4 (38/59)	51.3 (39/76)	8.5 (5/59)	7.9 (6/76)
Treatment-unaffected Ab against rHuPH20	0	100.0 (1/1)	0	0.0 (0/1)
Treatment-induced Ab against rHuPH20	62.8 (27/43)	69.6 (16/23)	2.3 (1/43)	0.0 (0/23)
Treatment-boosted Ab against rHuPH20	66.7 (6/9)	66.7 (6/9)	0.0 (0/9)	0.0 (0/9)
Unevaluable for Ab against rHuPH20	0	0.0 (0/1)	0	0.0 (0/1)

Ab=antibody(ies); AE=adverse event(s); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group and treatment group in the Stage B safety analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event(s); SC=subcutaneous(ly)

The impact of ADA against efgartigimod on safety was further evaluated by comparing the incidence of injection-related reactions and AEs of Injection site reactions across the ADA categories in Stages A and B. In Stages A and B, the occurrences of injection-related reactions and AEs of Injection site reactions were similar between participants who were positive for antibodies against rHuPH20 and those who were negative (Table 81 and Table 82, respectively).

Table 81: Percentage of Participants With Any Injection-Related Reaction or Injection Site Reaction by Participant Classification of Antibodies Against rHuPH20 in Study ARGX-113-1802 (Stage A Safety Analysis Set)

Participant classification	EFG PH20 SC % (n/N)	
	Injection-related reaction	Injection site reaction
Total	19.9 (64/322)	19.3 (62/322)
Negative for Ab against rHuPH20	18.3 (39/213)	18.8 (40/213)
Treatment-unaffected Ab against rHuPH20	25.9 (15/58)	20.7 (12/58)
Treatment-induced Ab against rHuPH20	21.4 (6/28)	28.6 (8/28)
Treatment-boosted Ab against rHuPH20	23.5 (4/17)	5.9 (1/17)
Unevaluable for Ab against rHuPH20	0.0 (0/6)	16.7 (1/6)

Ab=antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group in the Stage A safety analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Table 82: Percentage of Participants With Any Injection-Related Reaction or Injection Site Reaction by Participant Classification of Antibodies Against rHuPH20 in Study ARGX-113-1802 (Stage B Safety Analysis Set)

Participant classification	Injection-related reaction		Injection site reaction	
	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)	EFG PH20 SC % (n/N)	PBO PH20 SC % (n/N)
Total	9.9 (11/111)	5.5 (6/110)	14.4 (16/111)	6.4 (7/110)
Negative for Ab against rHuPH20	8.5 (5/59)	6.6 (5/76)	16.9 (10/59)	7.9 (6/76)
Treatment-unaffected Ab against rHuPH20	0/0	0.0 (0/1)	0/0	0.0 (0/1)
Treatment-induced Ab against rHuPH20	9.3 (4/43)	4.3 (1/23)	9.3 (4/43)	4.3 (1/23)
Treatment-boosted Ab against rHuPH20	22.2 (2/9)	0.0 (0/9)	22.2 (2/9)	0.0 (0/9)
Unevaluable for Ab against rHuPH20	0/0	0.0 (0/1)	0/0	0.0 (0/1)

Ab=antibody(ies); EFG PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; N=number of participants per participant classification group and treatment group in the Stage B safety analysis set; n=number of participants for whom the observation was reported; PBO=placebo; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Safety related to drug-drug interactions and other interactions

Clinical drug-drug interaction studies have not been performed with efgartigimod.

Efgartigimod may potentially affect the PK and/or PD of compounds that bind to the human FcRn (ie, immunoglobulin products, monoclonal antibodies, or antibody derivatives containing the human Fc domain of the IgG subclass).

Concurrent CIDP Therapies

Concurrent CIDP therapies were not allowed.

rHuPH20

Clinical studies to investigate a possible interaction between rHuPH20 and efgartigimod have not been performed. SC-administered rHuPH20 is used to increase the dispersion and absorption of other injected drugs (ie, efgartigimod when administered as efgartigimod PH20 SC). SC-administered rHuPH20 is transiently acting and is not measurable in circulation at clinically relevant doses. It has been demonstrated to exert no long-term local effects. rHuPH20 has a half-life in the skin of less than 30 minutes.

Vaccination

In ARGX-113-1802 and ARGX-113-1902, vaccination of participants with live-attenuated vaccines was prohibited within 28 days of screening (ARGX-113-1802) and during the studies. Any inactivated, subunit, polysaccharide, or conjugate vaccine at any time before screening was allowed.

As described in the gMG IV submission, no clinically relevant effect on PK and PD of therapeutic antibodies is expected when an antibody is given ≥2 weeks after the last dose of efgartigimod PH20 SC injection.

The safety of immunization with live or live-attenuated vaccines and the response to immunization with these vaccines during treatment with efgartigimod are unknown. It is recommended to administer all live and live-attenuated vaccines according to National immunization guidelines and ≥4 weeks before or ≥2 weeks after the last dose. For patients receiving efgartigimod, vaccination with live or live-attenuated vaccines is not recommended. Other vaccines may be administered as needed at any time during efgartigimod treatment.

Discontinuation due to adverse events

Study ARGX-113-1802 (Overall Population)

In Stage A, AEs leading to efgartigimod PH20 SC discontinuation were reported in 22 (6.8%; 46.9 events/100 PYFU) participants. Except for CIDP, which occurred in 15 (4.7%) participants, all AEs leading to efgartigimod PH20 SC discontinuation occurred in 1 (0.3%) participant each.

In Stage B, 3 (2.7%; 5.3 events/100 PYFU) participants in the efgartigimod PH20 SC arm and 1 (0.9%; 2.4 events/100 PYFU) participant in the placebo arm discontinued treatment because of an AE. All AEs leading to IMP discontinuation by PT occurred in 1 (0.9%) participant each in either arm.

Study ARGX-113-1902

AEs leading to efgartigimod PH20 SC discontinuation occurred in 9 (3.9%; 8.7 events/100 PYFU) participants in the total group of ARGX-113-1902 and occurred more frequently (≥5% difference between the treatment groups) in the 1802 Stage B PBO group than the 1802 Stage B EFG PH20 SC group (8 [8.0%; 14.6 events/100 PYFU] and 1 [1.0%; 1.7 events/100 PYFU] participant, respectively).

All AEs leading to efgartigimod PH20 SC discontinuation by PT occurred in 1 participant except for CIDP, which occurred in 4 (1.8%) participants.

Pooled Safety Data Set

A summary of AEs that led to efgartigimod PH20 SC discontinuation in ≥5% of the participants in the total pooled group is provided by MedDRA SOC and PT in Table 83.

AEs that led to efgartigimod PH20 SC discontinuation occurred in 34 (10.3%) participants. CIDP (19 [5.8%]) was the only AE leading to efgartigimod PH20 SC discontinuation that occurred in ≥5% of the participants in the total pooled group.

COVID-19 and COVID-19 pneumonia occurred in 2 (0.6%) participants. All other AEs leading to efgartigimod PH20 SC discontinuation occurred in 1 (0.3%) participant in the total pooled group.

Table 83: SC Pooling Block: AEs Leading to IMP Discontinuation (⩾5% of Participants in the Total Group) by MedDRA SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	PG1: Efgartigimod PH20 SC (only) (N=235; PYFU=155.1)		PG2: Efgartigimod PH20 SC (PBO PH20 SC) (N=94; PYFU=95.2)		PG3: Total pooled group (N=329; PYFU=250.3)	
	n (%)	m	n (%)	m	n (%)	m
≥1 AE leading to IMP discontinuation	26 (11.1)	26	8 (8.5)	11	34 (10.3)	37
Nervous system disorders	17 (7.2)	17	4 (4.3)	6	21 (6.4)	23
Chronic inflammatory demyelinating polyradiculoneuropathy	16 (6.8)	16	3 (3.2)	5	19 (5.8)	21

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; efgartigimod PH20 SC (only)=participants who received efgartigimod PH20 SC in ARGX-113-1802 Stage B and ARGX-113-1902; IMP=investigational medicinal product; ISS=integrated summary of safety; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the safety analysis set per pooling group; n=number of participants who reported ⩾1 event; PBO=placebo; PBO PH20 SC=participants who received placebo during Stage B of ARGX-113-1802 and reinitiated efgartigimod PH20 SC in ARGX-113-1902; PG=pooling group; PT=Preferred Term; PYFU=participant years of follow-up; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Unless specified, all AEs were treatment-emergent. AEs were coded using MedDRA version 25.1 (September 2022). PYFU was calculated as the sum of the follow-up times in the applicable period of all participants, expressed in years.

Post marketing experience

There are no postmarketing data for efgartigimod in patients with CIDP.

As of 16 Dec 2023, approximately 9158 patients with gMG have been exposed to efgartigimod in postmarketing settings. Cumulatively, 2700 serious ADRs (234 ADRs from spontaneous sources and 2466 ADRs from noninterventional studies and other solicited sources) and 1260 nonserious ADRs from spontaneous sources for efgartigimod IV and efgartigimod PH20 SC were reported to argenx.

Based on postmarketing safety information received up to 16 Dec 2023, no new safety concerns were identified for efgartigimod IV or efgartigimod PH20 SC in patients with gMG.

2.5.1. Discussion on clinical safety

The safety of efgartigimod alfa IV and efgartigimod PH20 SC is well known for the treatment of gMG. In this submission, both the posology and patient population differ from previous submissions. In gMG, the recommended dose is 1000 mg to be administered SC in cycles of once weekly injections for 4 weeks followed by a treatment-free period before a subsequent cycle, whereas in CIDP, the recommended dose

is 1000 mg administered SC as once-weekly injections. Therefore, the focus of this assessment is the clinically significant differences in safety for the CIDP patients compared to the known safety profile of efgartigimod alfa IV and efgartigimod PH20 SC.

Safety data

The clinical safety database for the treatment of CIDP is based on Study ARGX-113-1802 and ARGX-113-1902 (open-label extension). The safety database was grouped into three pooling blocks (PG1, PG2 and PG3). Safety data in gMG patients have previously been submitted and assessed.

The two studies ARGX-113-1802 and ARGX-113-1902 as well as PG3 (total pooled group) was used as the main clinical safety database. Safety for the pretreated population is mentioned in the relevant sections.

The potential carry over-effect in Stage A of e.g. IVIg or corticosteroids is considered minimal and without clinical significance for the safety evaluation due to the run-in period. However, the risk of a carry-over effect of efgartigimod PH20 SC treatment in Stage A into the placebo arm of Stage B may be of importance, considering that in the study IgG levels return to baseline-levels approximately 8 weeks after the final efgartigimod administration. The Applicant accounted for this potential carry-over effect by attributing AEs occurring up to 60 days after the last efgartigimod PH20 SC injection to efgartigimod PH20 SC. This approach is considered acceptable. Further, to account for the difference in exposure to placebo and efgartigimod PH20 SC, the Applicant provided event rates (events/100 PYFU).

Study ARGX-113-1802

In study ARGX-113-1802, 322 participants received at least 1 dose or part of a dose of efgartigimod PH20 SC in stage A. The mean (SD) duration of treatment was 5.2 (3.28) weeks.

Study ARGX-113-1902

In study ARGX-113-1902, 228 participants received at least 1 dose or part of a dose of efgartigimod PH20 SC: 29 participants who rolled over from the 1802 Stage A efgartigimod PH20 SC group, 99 from the 1802 Stage B efgartigimod PH20 SC group, and 100 from the 1802 Stage B placebo group. The mean (SD) duration of treatment was 29.92 (30.171) weeks.

Pooled Safety Data Set

In the total pooled group, 148 (45.0%) participants received at least 6 months of efgartigimod PH20 SC treatment, and 87 (26.4%) participants received at least 12 months of efgartigimod PH20 SC treatment.

Overall, the main safety database consisted of a total of 322 participants receiving at least 1 dose or part of a dose of efgartigimod PH20 SC, 148 CIDP patients were treated with efgartigimod PH20 SC for at least 6 months and 87 patients were treated with efgartigimod PH20 SC beyond 12 months. Despite the low prevalence of the disease (approximately 0.8 to 8.9 per 100 000), the safety database is considered small and does not fulfil the recommendations according to the current Guideline ("*To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300-600 patients should be adequate*." and "*100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base*" source: Note for Guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95), page 3). Rare events are not expected to be captured with the current safety database and overall, the safety data is hampered by the few patients included. The Applicant discussed further plans for ensuring adequate safety data for the treatment of CIDP. The OLE study ARGX-113-1902 is planned to continue through April 2027, and safety data will continue to be collected until then. Further post-marking safety data will be collected and the Applicant

considers routine pharmacovigilance activities are sufficient to further characterise the long-term safety profile of efgartigimod PH20 SC in patients with CIDP. This is considered acceptable.

Further, the Applicant has provided a second interim analysis (IA2) with a data cut-off date of 16 Feb 2024. With the new cut-off date, the mean (SD) treatment duration in the total group was 58.04 (33.759) weeks. Overall, the safety profile in the provided second interim analysis were consistent with the known safety profile of efgartigimod PH20 SC. No new safety concerns or adverse drug reactions (ADRs) to be included in the SmPC, are found based on provided data.

There are no data available on the use of efgartigimod PH20 SC as once-weekly injections for the treatment of CIDP beyond 2 years. As efgartigimod is intended to be used as a chronic therapy for both gMG and CIDP, long-term safety is included in the RMP as missing information and further data will be collected on the safety of long-term treatment as described above.

Adverse events

Studies ARGX-113-1802 and ARGX-113-1902

Overall, the frequencies of the different categories of AEs (e.g. AEs, SAEs, Grade ≥3 AEs etc.) in Stage A and Stage B of Study ARGX-113-1802 were similar or lower to the observed frequencies for efgartigimod PH20 SC in gMG patients in study ARGX-113-2001 (please refer to Vyvgart EPAR Procedure No. EMEA/H/C/005849/X/0003). However, deaths, SAEs and AEs for which the treatment were interrupted or discontinued were reported more frequently in study ARGX-113-1802 Stage A and Stage B compared to study ARGX-113-2001 in gMG patients. Deaths, SAEs, discontinuations and interruptions are assessed further below. In study ARGX-113-1902, for all the different categories of AEs and SAEs, the event rates decreased compared to ARGX-113-1802 Stage A. In the total pooled group, frequencies of AEs were similar to the observations in study ARGX-113-1802 and ARGX-113-1902.

Common adverse events

There was approximately a 5% higher percentage of participants with AEs of COVID-19 in the efgartigimod PH20 SC arm than the placebo arm in Stage B of ARGX-113-1802; however, the event rates were similar (35.3 and 33.3 events/100 PYFU, respectively). Further, the high percentage of participants with COVID-19 is expected since the studies ARGX-113-1802 and ARGX-113-1902 were conducted during the global COVID-19 pandemic.

CIDP recurrence were reported frequently in study ARGX-113-1802 Stage A (5.3%). However, the frequencies were the same in study ARGX-113-1802 Stage B in the placebo and efgartigimod PH20 SC arms (0.9%).

Overall, the most common AEs in the pretreated population were similar to the overall population in study ARGX-113-1802 Stage A and Stage B, except for nasopharyngitis, which occurred in 5 (10.4%) participants in the pretreated population versus 5 (4.5%) participants in the overall population. This difference is not considered clinically meaningful and the difference is properly due to small numbers in the pretreated population (n=48).

Overall, the most common AEs were consistent with the known safety profile of efgartigimod PH20 SC. No new safety concerns or ADRs to be included in the SmPC, are found based on the most common adverse reactions.

Deaths

4 fatal cases were reported in studies ARGX-113-1802 and ARGX-113-1902. Narratives have been provided for all 4 patients.

One patient died due to cardiac arrest, the investigator considered the SAE/AESI due to suspected COVID-19, this is considered plausible due to family members with COVID-19. Further, the patient had the vascular-related comorbidities that possible could have worsened the outcome of COVID-19.

Two patients died due to the SAE of Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP recurrence). In the first case the patient had two doses of efgartigimod PH20 SC. 33 hours after the first dose of efgartigimod PH20 SC the SAE was reported and his condition deteriorated further after the second dose. The investigator determined that the SAEs of CIDP were unlikely related to efgartigimod PH20 SC but related to deterioration of CIDP. In the second case the patient had received 43 doses of efgartigimod PH20 SC. The investigator considered the SAE of CTCAE grade 5 CIDP related to efgartigimod PH20 SC. The sponsor considered this event not related to efgartigimod PH20 SC and instead related to the progressive nature of CIDP. The Applicant discussed if the two fatal SAEs and the other SAEs of CIDP could be related to efgartigimod PH20 SC due to the mechanism of action. Disease fluctuations are common in patients with CIDP and these disease fluctuations could have contributed to the SAEs of CIDP in ARGX-113-1802 and ARGX-113-1902. Evidence suggests that IgG autoantibodies play a key role in CIDP. Given the mechanism of action of efgartigimod, treatment with efgartigimod PH20 SC is not a plausible explanation for CIDP worsening. Therefore, the Applicant considered none of the SAEs, including the 2 fatal events, of CIDP related to efgartigimod PH20 SC. This is acknowledged.

One patient died due to pneumonia. At the time of the event, the participant had received 4 doses of efgartigimod PH20 SC in Stage A and 39 doses of placebo in Stage B. The investigator considered the event possibly related to treatment. The sponsor assessed the SAE of Pneumonia as not related to treatment and indicated that the participant's age and medical history with vascular-related comorbiditieswere confounding factors. This is agreed.

Serious Adverse Events

Overall, the most frequent reported SAE were CIDP (20 (6.1%) participants in the pooled safety data set).

Adverse Events of Special Interest

Infections

Studies ARGX-113-1802 (Overall Population) and ARGX-113-1902

There was approximately a 5% higher percentage of participants with AEs of COVID-19 in the efgartigimod PH20 SC arm than the placebo arm in Stage B of ARGX-113-1802; however, as previously described, the event rates were similar, 35.3 and 33.3 events/100 PYFU, respectively.

Upper respiratory tract infection was more frequent in the placebo arm compared to the efgartigimod PH20 SC arm (10% vs. 1.8%). The reason for this is unclear, but will not be further pursued.

Pooled Safety Data Set

The most common AESIs by PT were COVID-19 (17,3%), nasopharyngitis (5.2%), and upper respiratory tract infection (9.4%).

The high percentage of participants with COVID-19 is expected since the studies ARGX-113-1802 and ARGX-113-1902 were conducted during the global COVID-19 pandemic. Nasopharyngitis has previously been evaluated in the initial application for efgartigimod IV, but not considered an ADR due to similar frequency in the placebo and efgartigimod IV arm. Upper respiratory tract infection is included in the SmPC as an ADR.

Serious AESIs occurred in 12 (3.6%) participants in the total pooled group. Overall, 4 (1.2%) participants had serious AESIs of COVID-19, 2 (0.6%) participants had COVID-19 pneumonia and 2 (0.6%) participants had Pneumonia.

AESIs that were considered related to efgartigimod PH20 SC by the investigator occurred in 33 (10.0%) participants. The most frequent related AESIs were upper respiratory tract infection (4.0%), COVID-19 (1.5%), and urinary tract infection (1.5%).

The incidence of AESIs relative to nadir IgG levels, showed that the frequency of AESIs in the >P75 quartile was lower (24.1%) than the other nadir quartiles (e.g. 50.0% for the nadir ≤P25). However, when looking at the event rates, the total number of AESIs were higher in groups of nadir IgG categories above the median than below the median. Overall, no clear trend was observed across IgG nadir quartiles.

Overall, the risk of infections and risk minimisation measures (RMM) is described in the SmPC and no new safety concerns were found based on the AESI evaluation.

Injection-Related Reactions and localized injection site reactions

Overall, the pattern of injection related reactions and localized injection site reactions were similar to the known safety profile of efgartigimod PH20 SC. The only new finding was a discontinuation due to injection site rash. The SmPC section 4.4 have been updated accordingly.

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)

AEs within the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) was reported in 6 participants.

All participants were >60 years of age, except for a participant (aged 35-55 years) with nonserious lipoma. Four of the participants had a relevant medical history.

Two of the events were considered possibly related by the investigator (squamous cell carcinoma and lipoma). The sponsor however, did not consider the squamous cell carcinoma as related since the participant's demographics could be likely contributors because squamous cell carcinoma is more common in males who are older and have light-coloured skin. The underlying CIDP could also be a confounder. Additionally, patients diagnosed with monoclonal gammopathy have a greater risk for developing several types of cancer, including nonmelanoma skin cancer, e.g., squamous cell carcinoma. The sponsor therefore determined that alternative etiologies provide a more plausible explanation for the SAE in this case.

Overall, the carcinogenetic potential of efgartigimod remain uncertain. Malignancies is already included in the safety specification of the RMP as an important potential risk (IPR).

Laboratory findings

Overall, the observed laboratory parameters, vital signs, ECG abnormalities and suicidality assessment do not raise any new safety concerns.

Safety in special populations

Age

Overall, 209 (82.6%) participants aged 18 to <65 years and 59 (77.6%) participants aged ≥65 years had AEs. In all the different AE categories, AEs were reported more frequently in the 18 to <65 years compared to the ≥65 years.

Baseline characteristic were overall similar between the two age groups. However, the median treatment duration was longer in the in the 18 to <65 years (21.0 weeks) compared to the ≥65 years category (15.0 weeks). This can explain the higher frequency of AEs in the 18 to <65-year age group.

Sex at Birth

No clinically meaningful difference in safety was found between male and female participants.

Race

Overall, 169 (78.2%) White participants and 79 (86.8%) Asian participants had AEs. In all the different AE categories, AEs were reported more frequently in Asian participants compared to White participants.

There were several differences in baseline characteristics that could explain the differences between the Asian and White participants (e.g. age; 26.4% of the White and 16.5% of the Asian participants were ≥65 years, median time since CIDP diagnosis; 3.04 years for White participants and 1.98 years for Asian participants, prior CIDP therapy; IVIg and SCIg for 53.2% of White participants and 37.4% of Asian participants and corticosteroids for 17.1% and 28.6% of White and Asian participants).

Body Weight

There was a trend toward an increasing percentage of participants with AEs with increasing body weight: 78.2% in the 50 to <75 kg group, 82.4% in the 75 to <100 kg group, and 91.7% in the 100 to <125 kg group. However, the median treatment duration was also increasing with increasing body weight: 15.0 weeks in the 50 to <75 kg group, 24.0 weeks in the 75 to <100 kg group and 37.5 weeks in the 100 to <125 kg group. This can explain the higher frequency of AEs with increasing bodyweight.

Hepatic Impairment

There have been no clinical studies of efgartigimod in participants with hepatic impairment, and the safety of efgartigimod in this population is unknown. Due to the nature of the product, an impact of hepatic impairment is not expected.

Renal Impairment

There haven’t been any clinical studies of efgartigimod in participants with renal impairment.

There were insufficient data to evaluate the effect of moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m2) and severe renal impairment (eGFR <30 mL/min/1.73 m²) on the safety of efgartigimod PH20 SC in participants with CIDP in ARGX-113-1802.

In studies in participants with gMG, safety data were analysed by baseline renal function based on eGFR value. A review of the clinical safety data showed that mild renal impairment did not impact the safety profile of efgartigimod PH20 SC.

Use in patients with moderate and severe renal impairment is included as missing information in the RMP.

Immunogenicity

ADA and Nab against efgartigimod

Overall, ADA and Nab against efgartigimod were lower in the efgartigimod PH20 SC arm compared to the previous studies in gMG patients. However, ADA and Nab were higher in the placebo arm of Stage B after treatment withdrawal. The incidence of ADA or NAb against efgartigimod with continuous dosing compared with cyclic dosing is likely lower due to differences in posology and timing of sampling. Other

factors (e.g., patient population, concomitant medication, and treatment duration) could have also contributed to the differences in the incidence of ADA and NAb against efgartigimod between participants with CIDP and gMG.

Based on the provided data, there was no impact of ADA against efgartigimod on AEs, SAEs, injection-related reactions or Injection site Reactions.

ADA and Nab against rHuPH20

As the incidence of NAb was higher in stage B of the 1802 study than previously observed in gMG studies, a set of additional NAb confirmatory assays (screening, confirmatory and titer) was implemented. After full confirmatory analysis, the samples that were screened positive, were considered false positives due to low titers.

Overall, the incidence and prevalence of ADA and Nab (after confirmatory analysis) against rHuPH20 were similar to previous studies in gMG patients.

Overall, the immunogenicity data does not raise any concerns regarding safety, since there was no difference in the overall AE and SAE profile between the ADA positive and ADA negative patients.

Drug-drug interactions

Due to its mode of action, efgartigimod affects the elimination of therapeutic IgGs, including IVIg. Concomitant use of these compounds has not been evaluated in any of the clinical studies. A recommendation to postpone initiation of treatment with these products and a precaution to monitor for efficacy response is reflected in the SmPC section 4.5. The use of efgartigimod with monoclonal antibodies is included in the RMP as missing information.

The safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are currently unknown. Effect on vaccination efficacy and the use of live/attenuated Vaccines is included in the RMP as missing information.

Discontinuations due to adverse events

AEs for which the treatment were discontinued (6.8%) were reported more frequently in study ARGX-113-1802 Stage A compared to study ARGX-113-2001 in gMG patients (3.6%). In Stage B, 2.7% of the participants in the efgartigimod PH20 SC arm and 0.9% of the participant in the placebo arm discontinued treatment because of an AE.

Overall, the most common AE leading to efgartigimod PH20 SC discontinuation was CIDP (4.7% participants). The Applicant discussed if discontinuations due to CIDP could be related to efgartigimod PH20 SC. As stipulated in the ARGX-113-1802 protocol, participants in Stage A had to discontinue from the study if they had an aINCAT deterioration of ≥2 points from Stage A baseline. Many of these aINCAT deteriorations were reported as an AE. Consequently, instead of discontinuing the study due to "lack of efficacy," the protocol requirement led to a higher reporting of the AE "CIDP worsening." Therefore, the Applicant considered none of the AEs of CIDP leading to discontinuation related to efgartigimod PH20 SC. Serious infections and malignancies are IPR in the Summary of PSUR safety concerns. This is acknowledged.

In Study ARGX-113-1902, AEs leading to efgartigimod PH20 SC discontinuation occurred in 3.9% of the participants.

Post marketing experience

Overall, the post-marketing safety data are in line with the known safety profile and what could be expected for the treated patient group. No conclusions can be drawn on the serious adverse events due to limited data. No new safety concerns are raised.

2.5.2. Conclusions on clinical safety

Overall, available safety data from the clinical development programme in CIDP is consistent with the known safety profile for efgartigimod PH20 SC in gMG.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable.

Safety concerns

Table 84: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections Malignancies
Missing information	Use in pregnant women Use with live/attenuated vaccines Use with monoclonal antibodies Use in patients with moderate and severe renal impairment Long-term safety of efgartigimod treatment Use in immunocompromised patients

Pharmacovigilance plan

Table 85: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Post-authorization safety study/ ARGX-113-PASS-2208 Planned	To evaluate the overall long-term safety of efgartigimod, including the occurrence of serious infections, in patients with gMG treated with efgartigimod compared with patients with gMG not exposed to efgartigimod.	• Long-term safety of efgartigimod treatment • Serious infections • Malignancies • Use with live/attenuated vaccines • Use with monoclonal antibodies • Use in patients with moderate and severe renal impairment • Use in immunocompromised patients	Protocol	14 Dec 2023
			First interim report	Q2 2028
			Final report	Q2 2035
Pregnancy post-authorization safety study/ ARGX-113-PAC-2206 Planned	To assess maternal, fetal, and infant outcomes following exposure to efgartigimod during pregnancy and/or breastfeeding	• Use in pregnant women	Protocol	14 Dec 2023
			First Interim report	Q4 2024
			Final report	Q4 2034
Malignancy post-authorization safety study/ ARGX-113-PASS-2316 Planned	To evaluate the long-term risk of malignancies in patients with MG treated with efgartigimod compared with patients with MG receiving any other MG therapy who do not have malignancy history in the lookback period.	• Malignancies	Protocol	TBC
			First interim report	TBC
			Final report	TBC

gMG=generalized myasthenia gravis; PASS=post-authorization safety study; Q2=second quarter; Q4=fourth quarter; TBC=to be confirmed

Risk minimisation measures

Table 86: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infections	Routine risk minimization measures: • SmPC section 4.4 and 4.8 • PL section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Malignancies	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire for malignancies Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208) • Malignancy PASS (ARGX-113-PASS-2316)
Use in pregnant women	Routine risk minimization measures: • SmPC section 4.6 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Pregnancy PASS (ARGX-113-PAC-2206)
Use with live/attenuated vaccines	Routine risk minimization measures: • SmPC section 4.4 • SmPC section 4.5 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Use with monoclonal antibodies	Routine risk minimization measures: • SmPC section 4.5 • PL section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Use in patients with moderate and severe renal impairment	Routine risk minimization measures: • SmPC section 4.2 and 5.2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Long-term safety of efgartigimod treatment	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)
Use in immunocompro-mised patients	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• PASS of patients treated with efgartigimod (ARGX-113-PASS-2208)

PASS=post-authorization safety study, PL=package leaflet, SmPC=summary of product characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2. 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s).

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The subject of this application is efgartigimod for SC administration in patients with CIDP with active disease. CIDP is a severe, debilitating, progressive autoimmune disease of the peripheral nervous system, characterized by muscle weakness and sensory disturbance caused by peripheral nerve demyelination. The estimated prevalence of CIDP ranges from 0.8 to 8.9 per 100 000 persons. A key feature of CIDP is evidence of demyelination, although variable degrees of secondary axonal loss are also common. The extent of axonal loss is a primary determinant of long-term disability and irreversible nerve injury, and it may cause a substantial disease burden. The pathophysiology of CIDP remains unclear, but several lines of evidence indicate that both cellular and humoral components of the immune system are involved. Efgartigimod blocks the FcRN and reduces the levels of circulating disease-causing IgG antibodies.

3.1.2. Available therapies and unmet medical need

Early treatment is important for patients with CIDP. The goal is to stop the immune attack against the myelin sheath of peripheral nerves to minimize irreversible axonal degeneration and reduce long-term disability. CIDP guidelines recommend IVIg/SCIg or corticosteroids as the first-line treatment. Despite these current treatment options many patients with CIDP continue to suffer from debilitating symptoms, have disease fluctuation and a substantial treatment burden, and often require chronic therapy. Current treatment options can be associated with lengthy infusion durations and severe complications such as thrombosis, acute renal dysfunction, and other undesirable effects such as weight gain and osteoporosis, limiting long-term administration. IVIg/SCIg are both dependent on plasma donors with potential for supply chain shortages.

3.1.3. Main clinical studies

The pivotal phase 2 study ARGX-113-1802 was a prospective, multisite study on the efficacy, safety, tolerability, immunogenicity, PK and PD of efgartigimod PH20 SC in adult participants diagnosed with probably or definite CIDP. The study was conducted as a randomized withdrawal study in 2 treatment stages: an open-label Stage A in which responders to efgartigimod PH20 SC were identified, and a randomized-withdrawal, double-blinded, placebo-controlled Stage B. The long-term efficacy of efgartigimod PH20 SC was evaluated in the ongoing, open-label study ARGX-113-1902, which is an extension of ARGX-113-1802.

In both Stage A and Stage B the efficacy was evaluated in the overall population and in a pre-defined subgroup, the pretreated population. The pretreated population was defined as participants who received CIDP therapy within 6 months prior to screening and had a CDAS score of at least 4, indicating active disease, at screening.

3.2. Favourable effects

The primary endpoint in Stage A was the percentage of participants with confirmed ECI, e.g. efgartigimod responders. The proportion of responders (ECI in Stage A) was 66.5% (95% CI: 61-71.6) in the overall population and 67.6% (95% CI: 59.2-75.3) in the pre-treated population. The median (min, max) time to confirmed ECI was 31 (23-43) days in the pre-treated population and 43 (31.0-51.0) days in the overall population.

The primary endpoint in Stage B was time to first deterioration on the aINCAT score. Participants in Stage B, treated with efgartigimod, had a reduced risk of relapse compared to placebo. In the overall population, relapse occurred in 31 patients (27.9%) in the efgartigimod group versus n=59 (53.6%) in the placebo group with a HR of 0.394 (95% CI: 0.253-0.614). In the pretreated population relapse was also more frequent in the placebo group compared to the efgartigimod group (68.1% versus 27.1%, respectively). This corresponds to a HR of 0.269 (95% CI 0.138-0.523).

3.3. Uncertainties and limitations about favourable effects

In the absence of a placebo arm in stage A in the pivotal trial ARGX-113-1802, short-term efficacy of efgartigimod versus placebo was not established. In stage A of the pivotal trial, responders to efgartigimod were identified, and given that only responders and patients who tolerate the drug in Stage A are selected to enter the randomized controlled phase, Stage B, significant bias was introduced. Particularly, being an efgartigimod responder in Stage A is considered to correlate with the primary endpoint (relapse upon withdrawal of efgartigimod) of the randomized controlled arm of the trial, Stage B. This results in enrichment and may lead to an overestimation of the treatment effect. Thus, the present study design mainly answers the question of whether an efgartigimod responder continues to respond to efgartigimod, rather than the question of whether efgartigimod is an efficacious treatment for CIDP. Further bias may be introduced by a rebound effect (e.g. drastic clinical worsening) after sudden cessation of CIDP treatment prior to Stage A. Presence of a rebound effect with some, spontaneous stabilization in Stage A, may overestimate the efficacy of efgartigimod. The study design has a lack of external validity making it difficult to define the target population. To meet these concerns of generalizability the Applicant introduced a phrase in the SmPC specifically advising clinical evaluation of treatment response after 3-6 months.

However, the lack of placebo-controlled data in Stage A was justified by the Applicant due to the combination of ethical and feasibility challenges, disease rarity and severity. To further substantiate efficacy, the Applicant provided data from historical placebo controls from several historical, placebo-

controlled studies. Major methodological differences between these studies and ARGX-113-1802 exist and makes comparison and extrapolation of placebo response rates challenging. Nevertheless, historical studies are generally aligned at placebo response rates of about 20% or less. In addition, the Applicant provided a mechanistic rationale for the use of efgartigimod in CIDP (reduction of pathological immunoglobulin G). Therefore, even if the effect size of efgartigimod in CIDP versus placebo could not be isolated due to the absence of an internal control, the overall available evidence supports that efgartigimod is efficacious in CIDP.

3.4. Unfavourable effects

Overall, the frequencies of the different categories of AEs (e.g. AEs, SAEs, Grade ≥3 AEs etc.) in Stage A and Stage B of Study ARGX-113-1802 were similar or lower to the observed frequencies for efgartigimod PH20 SC in gMG patients in study ARGX-113-2001 (please refer to Vyvgart EPAR Procedure No. EMEA/H/C/005849/X/0003). However, deaths, SAEs and AEs for which the treatment were interrupted or discontinued were reported more frequently in study ARGX-113-1802 Stage A and Stage B compared to study ARGX-113-2001 in gMG patients.

Four fatal cases were reported in studies ARGX-113-1802 and ARGX-113-1902. One patient died due to cardiac arrest, two patients died due to the SAE of CIDP recurrence and one patient died due to pneumonia. In one of the CIDP cases and in the pneumonia case, the investigator considered the event related to efgartigimod PH20 SC. None of the fatal event were considered related to efgartigimod PH20 SC by the sponsor.

With regard to SAEs, 51 (15.5%) participants had SAEs in the total pooled group. SAEs considered related to efgartigimod PH20 SC occurred in 10 (3.0%) participants. SAEs of CIDP occurred in 20 (6.1%) participants. COVID-19 in 4 (1.2%) participants, and COVID-19 pneumonia, pneumonia, and fall, each in 2 (0.6%) participants. All other SAEs by PT occurred in 1 participant.

AEs for which the treatment were discontinued (6.8%) were reported more frequently in study ARGX-113-1802 Stage A compared to study ARGX-113-2001 in gMG patients (3.6%). In Stage B, 2.7% of the participants in the efgartigimod PH20 SC arm and 0.9% of the participant in the placebo arm discontinued treatment because of an AE. Overall, the most common AE leading to efgartigimod PH20 SC discontinuation was CIDP (4.7% participants).

The most common AESIs by PT were COVID-19 (17,3%), nasopharyngitis (5.2%), and upper respiratory tract infection (9.4%). Overall, the risk of infections was consistent with previous studies in gMG patients.

With regard to the most common adverse events, there was approximately a 5% higher percentage of participants with AEs of COVID-19 in the efgartigimod PH20 SC arm than the placebo arm in Stage B of ARGX-113-1802; however, the event rates were similar (35.3 and 33.3 events/100 PYFU, respectively). Further, the high percentage of participants with COVID-19 is expected since the studies ARGX-113-1802 and ARGX-113-1902 were conducted during the global COVID-19 pandemic.

Overall, the most common AEs were consistent with the known safety profile of efgartigimod PH20 SC.

In conclusion, the safety profile for efgartigimod PH20 SC in CIDP patients were consistent with the known safety profile of efgartigimod PH20. Infections are a known safety concern for efgartigimod and serious infections is included in the RMP as an IPR.

3.5. Uncertainties and limitations about unfavourable effects

The main safety database consisted of a total of 322 participants receiving at least 1 dose or part of a dose of efgartigimod PH20 SC, 148 CIDP patients were treated with efgartigimod PH20 SC for at least 6 months and 87 patients were treated with efgartigimod PH20 SC beyond 12 months. There are no data available on the use of efgartigimod PH20 SC as once-weekly injections for the treatment of CIDP beyond 2 years. As efgartigimod is intended to be used as a chronic therapy for both gMG and CIDP, long-term safety is included in the RMP as missing information and further data will be collected on the safety of long-term treatment.

Efgartigimod appears to be associated with a higher risk of infection, which is in accordance with its mechanism of action as a FcRn antagonist, which causes transient reduction in IgG levels. So far, during the clinical development, the majority of infectious events have been mild or moderate in severity and non-serious. However, more serious infections, including opportunistic infections, cannot be ruled out when more patients are exposed to the drug, especially for long periods. 'Serious infections' are included in the RMP as an IPR and a PASS is ongoing.

AEs within the SOC neoplasms benign, malignant and unspecified (incl. cysts and polyps) was reported in 6 participants. The carcinogenetic potential of efgartigimod remain uncertain. Malignancies is already included in the safety specification of the RMP as an IPR.

Further missing data includes use in pregnant women, use with live/attenuated vaccines, use with monoclonal antibodies, use in patients with moderate and severe renal impairment and use in immunocompromised patients. These were all discussed during the initial marketing authorisation application for the IV formulation and are also applicable to the SC formulation in CIDP patients. The missing information is included in the RMP and will be addressed in a PASS.

3.6. Effects Table

Table 87: Effects Table for efgartigimod PH20 SC in CIDP (data cut-off: 15 June 2023)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects: Stage A						
Treatment responder (primary endpoint) (overall and pretreated)	Clinical improvement (aINCAT, I-RODS, grip strength)	%	Overall: 66.5 Pre-treated: 67.6	N/A	Overall 95% CI: 61.0-71.6 Pre-treated 95% CI: 59.2-75.3 Methodological concerns: Open label, lack of internal validity (no placebo control). Rebound effect with spontaneous stabilization in Stage A (bias favours efgartigimod).	(1)
Time to treatment response (overall and pre-treated)	Clinical improvement (aINCAT, I-RODS, grip strength)	days	Overall: Median 43 Pretreated: Median 31	N/A	Overall 95% CI: 95% CI: 31.0-51.0 Pre-treated 95% CI: 95% CI: 23.0-43.0 Methodological concerns stated above.	(1)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects: Stage B						
Prevention of relapse **(primary endpoint)** (overall and pretreated)	Clinical deterioration rate (relapse) measured by aINCAT deterioration compared to Stage B baseline	%	Overall: 27.9 Pretreated: 27.1	Overall: 53.6 Pretreated: 68.1	HR (95% CI) overall: 0.394 (0.253-0.614) HR (95% CI) pretreated: 0.269 (0.138-0.523) Methodological concerns: Overestimation of treatment effect (after enrichment in Stage A). Lack of external validity. Response in Stage A may be correlated to the primary endpoint in Stage B (bias favours efgartigimod)	(1)
Unfavourable Effects						
⩾ 1 AEs	Incidence	%	64.0	56.4		(2)
⩾ 1 SAE	Incidence	%	5.4	5.5		(2)
⩾ 1 AESI	Incidence	%	31.5	33.6		(2)
AE COVID-19	Incidence	%	17.1	12.7		(2)
AE Injection site bruising	Incidence	%	5.4	0.9		(2)
AE Injection site erythema	Incidence	%	5.4	0.0		(2)
AE Headache	Incidence	%	3.6	1.8		(2)
AE CIDP	Incidence	%	0.9	0.9		(2)
SAE CIDP	Incidence	%	6.1			(3)
AE COVID-19	Incidence	%	17.3			(3)
AE Nasopharyn-gitis	Incidence	%	5.2			(3)
AE URTI	Incidence	%	9.4			(3)

Abbreviations: URTI: Upper respiratory tract infection

Notes: (1) ARGX-113-1802, Mod. 5.3.5 – Summary of main efficacy results (2) Study ARGX-113-1802 Stage B, (3) Pooled Safety Data Set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The concerns related to the design of the single pivotal trial ARGX-113-1802 are of significant importance, since in the absence of a placebo controlled study, effect size of efgartigimod in CIDP versus placebo could not be isolated . The Applicant has justified use of historical placebo controls. In addition, the concerns raised on the magnitude of placebo effect has been solved and the historical placebo response rates to substantiate the results of Stage A are considered justified. The presented placebo

response rates are sufficiently consistent. The overall available evidence supports that efgartigimod is efficacious in CIDP.

With the caution needed due to the limitations of the safety database, particularly in the long-term, it appears that the safety profile of efgartigimod PH20 SC in patients with CIDP is manageable and consistent with the known safety profile. Overall, available safety data from the clinical development program show that efgartigimod was generally well tolerated. Infections are a known safety concern for efgartigimod and serious infections is included in the RMP as an IPR.

3.7.2. Balance of benefits and risks

Given the mechanistic rationale, the large margin to the historical placebo effect and the unmet need in a difficult to study population it is considered sufficiently documented that efgartigimod is efficacious in CIDP. In general, treatment with efgartigimod PH20 SC was well tolerated, with a low incidence of SAEs, severe AEs and AEs leading to treatment discontinuation. Four deaths were reported, but none of them were considered as related to efgartigimod treatment. Efgartigimod appears to be associated with a higher risk of infections. Although available data do not seem to indicate an increased risk of serious infections and malignancies with efgartigimod over time related to its immunosuppressive effects, the limited number of patients with long-term exposure prevents any sound conclusion on these risks. The ongoing PASS is expected to provide additional data about these risks.

Overall, the safety profile of efgartigimod PH20 SC was consistent with the known safety profile in gMG patients.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of efgartigimod PH20 SC in CIDP is positive

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the monotherapy treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins for Vyvgart, based on final results from study ARGX-113-1802; this

is a pivotal study to investigate the efficacy, safety and tolerability of efgartigimod PH20 SC in adult patients CIDP; and based on interim results from study ARGX-113-1902; this is an open-label extension study of the ARGX-113-1802 trial to investigate the long-term safety, tolerability and efficacy of efgartigimod PH20 SC in patients with CIDP. As a consequence, sections 4.1, 4.2. 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. RMP is updated to version 3.0 In addition, the MAH took the opportunity to implement editorial changes to the SmPC and to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.