14 September 2023
EMA/CHMP/443026/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyvgart

International non-proprietary name: Efgartigimod alfa

Procedure No. EMEA/H/C/005849/X/0003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AChE	Acetylcholinesterase inhibitors
AChR	Anti-acetylcholine Receptor
ADA	Antidrug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Events
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANOVA	Analysis of covariance
ARS	Assay Reference Standard
AST	Aspartate Aminotransferase
$AUC_{0\text{-}inf}$	Area Under the Concentration-time curve from time zero to infinity
$AUC_{0\text{-}last}$	Area Under the Concentration-time curve from time 0 to the last quantifiable concentration
$AUC_{0\text{-}xh}$	Area Under the Concentration-time curve from time zero to x hours postdose
AUEC	Area Under the Effect Curve
BE	Bioequivalence
BE	Bulk Enzyme
BL	Baseline
BP	Blood pressure
BSE	Bovine Spongiform Encephalopathy
CCI	Container Closure Integrity
CCS	Container Closure System
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI(s)	Confidence Interval(s)
CL(/F)	(apparent) systemic clearance
Cmax	Maximum observed concentration
CPP	Critical Process Parameter
CPV	Continued Process Verification

CQA	Critical Quality Attributes
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Concentration at the end of a dosing interval
CV	Variability
DDI	Drug-drug Interaction
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EC	European Commission
EC50	Concentration in the effect compartment providing half of the maximum effect
ECG	electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOPC	End-Of-Production Cell Bank
EU	European Union
FcRn	Neonatal Fc Receptor
FDA	Food and Drug Administration
FMEA	Failure Modes And Effects Analysis
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
gMG	Generalized Myasthenia Gravis
GMP	Good Manufacturing Practice
GoF	Goodness of Fit
HC	High Concentration
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IIV	Interindividual Variability
IM	Intramuscular
IMP	Investigational Medicinal Product
IPC	In-Process Control
IV	Intravenous

IVIg	Intravenous immunoglobulins
Ka	first order absorption rate
keo	first-order delay rate constant
KLH	*Keyhole limpet hemocyanin*
kout	degradation rate
LC	Low Concentration
LIVCA	Limit Of *In Vitro* Cell Age
LS	Least Squares
(m)ITT	(modified) Intent-To-Treatment
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QoL15r	15-item Quality of Life scale for Myasthenia Gravis
MuSK	Muscle-Specific receptor tyrosine Kinase
Nabs	Neutralizing Antibodies
NI	Noninferiority
NOAEL	No Observed Adverse Effect Level
NSIDs	Nonsteroidal immunosuppressive drugs
PA	Performance Attributes
pcVPCs	prediction corrected Visual Predictive Checks
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PL	Package leaflet
PLEX	Plasmapheresis/plasma exchange

popPK	Population PK
PPQ	Process Performance Qualification
PRS	Primary Reference Standard
PS20	Polysorbate 20
PT	Preferred Term
PTE	Proportion of the treatment effect
q7d	Once every 7 days / weekly
QA	Quality Attributes
QbD	Quality By Design
QC	Quality Control
QMG	Quantitative Myasthenia Gravis
QTPP	Quality Target Product Profile
REC	Recommendation
rHuPH20	Recombinant Human Hyaluronidase PH20
RMP	Risk Management Plan
RO	Receptor Occupancy
SAP	Statistical analysis plan
SC	Subcutaneous
SE	Standard error
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
$t_{½,eff}$	Effective elimination half-life
$t_{½,z}$	Terminal elimination half-life
TEAEs	Treatment-emergent adverse events
t_{max}	Time of maximum observed concentration
TSE	Transmissible Spongiform Encephalopathy
UF/DF	Ultrafiltration/Diafiltration
WCB	Working Cell Bank
WRS	Working Reference Standard

1. Background information on the procedure

1.1. Submission of the dossier

Argenx submitted on 10 November 2022 an extension of the marketing authorisation.

The MAH applied for an addition of a new strength (1000 mg), addition of a new pharmaceutical form (solution for injection) and an addition of a new route of administration (subcutaneous use).

The MAH applied for the following indication for Vyvgart the new strength and new pharmaceutical form:

Vyvgart is indicated as an add on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti acetylcholine receptor (AChR) antibody positive.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) points (c) (d) (e) - Extensions of marketing authorisations.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0392/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP /0392/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher

The application was received by the EMA on	10 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 February 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 February 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	30 March 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	16 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 June 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 July 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	20 July 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	11 August 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vyvgart on	14 September 2023
The CHMP adopted a report on similarity of Vyvgart with Soliris on (see Appendix on similarity)	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Generalized myasthenia gravis is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic immunoglobulin G (IgG) autoantibodies, binding to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction, which causes debilitating and potentially life-threatening muscle weakness.

2.1.2. Epidemiology

The disease presents with two peaks of incidence, below or above the age of 50, termed early-onset MG and late-onset MG, respectively. The incidence ranges from 0.3 to 2.8 per 100,000 and it is estimated to affect more than 700,000 people worldwide.

Myasthenia gravis is considered to affect less than 2 in 10,000 people in the European Union (EU).

2.1.3. Aetiology and pathogenesis

MG is considered a model antibody-mediated autoimmune disease, since in most cases the autoantibodies and target antigens are well-characterized. The diagnosis of myasthenia gravis is confirmed by the combination of relevant symptoms and signs and a positive test for specific autoantibodies (antibodies against acetylcholine receptors ~85%, muscle-specific kinase ~6%, and lipoprotein receptor– related protein ~2%). The pathogenicity of all these autoantibodies has been shown by the development of passive transfer experimental autoimmune MG when injected into laboratory animals and by the improvement of patients' symptoms following plasmapheresis. Some patients do not have detectable antibodies against any of these antigens, being referred to as seronegative MG. Antibodies against various other extracellular or intracellular targets are found in several MG patients (e.g., agrin, colQ, Kv1.4, titin). MG pathogenesis, its clinical presentation and the response of patients to therapy vary depending on the pattern of autoantibodies detected.

The pathogenic actions of IgG autoantibodies include functional blockade of AChR, accelerated internalization and degradation of AChR, and activation of the complement system. These pathogenic actions result in reduced density of functional AChR and simplification of the neuromuscular junction, leading to failure of neuromuscular transmission. Anti-AChR autoantibodies are of the IgG1 and IgG3 subtypes. Anti-MuSK (Muscle-Specific receptor tyrosine Kinase) autoantibodies are IgG4 subtype and do not activate the complement pathway.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

In about two-thirds of patients, the first symptom is weakness of extrinsic ocular muscles. In 1 of 10 MG patients, symptoms remain limited to extrinsic ocular muscles (ocular myasthenia gravis). However, in more than 80% of patients, the symptoms progress within 2 years to affect other bulbar muscles as well as limb muscles (gMG). The generalized muscle weakness leads to difficulties in mobility, speech, swallowing, and vision, as well as impaired respiratory function and extreme fatigue. Up to 20% of patients experience

potentially life-threatening myasthenic crisis, with respiratory failure requiring mechanical ventilation. In approximately 90% of patients, IgG autoantibodies are detected in the serum, with the most common being against AChR. The remaining 10% of patients may have autoantibodies that are undetectable, at a concentration less than the assay's lower limit of detection, or against epitopes undetectable in the assay or that bind an unknown target. In patients with undetectable autoantibodies, the diagnosis is determined through neurophysiological examination, including repetitive nerve stimulation or single-fiber electromyography, and symptomatic improvement following treatment with acetylcholinesterase (AChE) inhibitors.

The Myasthenia Gravis Foundation of America (MGFA) Clinical Classification categorizes patients according to clinical evaluation, which in increasing severity can be, ocular MG; mild, moderate, severe generalized symptoms of MG; MG that requires intubation. Validated symptom scales including the Myasthenia Gravis Activities of Daily Living (MG-ADL), Quantitative Myasthenia Gravis (QMG), and Myasthenia Gravis Composite (MGC) scores are used to assess and track the clinical and functional burden of MG, whereas the 15-item Quality of Life scale for Myasthenia Gravis (MG-QoL15r) measures the impact of MG on the patient's quality of life.

2.1.5. Management

Current treatment options include acetylcholinesterase inhibitors, short-term immune therapies such as plasmapheresis or intravenous immunoglobulin (IVIg), and long-term immune therapies with immunosuppressive agents such as corticosteroids, azathioprine, cyclosporine, and mycophenolate, but tacrolimus, methotrexate, and cyclophosphamide are also used. Thymectomy is also a treatment option. Monoclonal antibodies such as eculizumab, ravulizumab or rituximab are used for more refractory cases. Efgartigimod IV was approved in 2022 and the therapeutic area is expanding.

Plasmapheresis/plasma exchange (PLEX) and IVIg are typically used for treatment of severe exacerbations of gMG.

A considerable variation exists in the management of gMG, and treatment is not standardized. There is no consensus on the choice of immunosuppressive agent and widespread use of particular agents remains, even though available data from a randomized controlled study do not support their use in MG (Sussman 2018[1], Hart 2007[2], Schneider-Gold 2019[3]). With the exception of AChE inhibitors, azathioprine, the complement inhibitors eculizumab and ravulizumab, and the FcRn antagonist efgartigimod IV, which have received regulatory approval in Europe for the treatment of gMG subgroups, all other existing therapies are used off-label.

The use of corticosteroids for the treatment of gMG is based on observational rather than high-quality randomized controlled clinical studies (Sieb 2014[4], Schneider-Gold 2019[5]). The immunosuppressants cyclosporin and tacrolimus have each failed to significantly reduce the doses of corticosteroid required to

[1] Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. The association of British neurologists' myasthenia gravis guidelines. Ann N Y Acad Sci. 2018;1412(1):166-169
[2] Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. Cochrane Database Syst Rev. 2007;(4):CD005224.
[3] Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242.
[4] Sieb JP. Myasthenia gravis: an update for the clinician. Clin Exp Immunol. 2014;175(3):408-418.
[5] Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242

maintain disease control in prospective double-blinded studies (Tindall 1993[6], Yosikawa 2011[7]). In a phase 3 study, mycophenolate mofetil was not superior to placebo in maintaining MG control during a 36-week schedule of prednisone tapering (Sanders 2008[8]). In the BeatMG study, rituximab failed to meet its primary endpoint, assessing the percentage of patients who achieve a ≥75% reduction in mean daily prednisone dose in the 4 weeks prior to week 52 and have clinical improvement of no worsening of symptoms (≤2-point increase in MGC score), in the rituximab and placebo arms.

Current therapies for gMG either provide inadequate control of the disease or are associated with an increased risk of serious side effects or patient inconvenience, which may limit their use.

AChE inhibitors are short-acting and often need to be taken several times daily. Their efficacy in AChR-Ab seronegative patients is limited (Sanders 2016[9]). Furthermore, patients rarely achieve amelioration of symptoms with AChE inhibitors alone and the majority of patients require additional treatment with unlicensed steroids and nonsteroidal immunosuppressive drugs (NSIDs). The use of AChE inhibitors is also constrained by the well-defined cholinergic side effects which limit the doses that can be tolerated, and additional treatment is often required to manage adverse effects. For example, the pyridostigmine Summary of Product Characteristics (SmPC) makes clear that atropine or other anticholinergic drugs may be necessary to counteract the muscarinic effects.

Eculizumab is indicated in patients who have refractory gMG and who are AChR-Ab seropositive. In addition, the eculizumab SmPC carries a warning for the risk of serious meningococcal infections, and vaccination is essential prior to treatment. The Soliris European Public Assessment Report estimates that the gMG patient subset for which eculizumab is indicated represents approximately 10% of patients with generalized disease. This is supported by 2 European publications:

• UK retrospective Clinical Practice Research Datalink and Hospital Episode Statistics databases study: 66 of 1149 (5.7%) patients met criteria for refractory gMG

• Austria tertiary centre chart review: 14 of 126 patients (11.1%) met criteria of treatment-refractory MG

Long-term use of corticosteroids (e.g., prednisone) is associated with serious side effects such as hypertension, diabetes, osteoporosis, and gastrointestinal effects. Long-term use of NSIDs like azathioprine, MMF, and methotrexate may be associated with severe side effects that vary by agent but can include liver and bone marrow toxicities, malignancies, and increased risk of infection. NSIDs have an extended delay in their onset of action; azathioprine is usually only effective after 12 months, and mycophenolate requires 6 to 12 months of treatment before being effective. PLEX is a lengthy and burdensome procedure and is usually conducted in a hospital or specialized clinical setting. IVIg use is limited in patients who are at risk of renal dysfunction and those who have a history of hypertension or risk factors for thrombotic events. IVIg use is further limited by potential shortages. Shortages in IVIg have been reported in Europe, with measures implemented to restrict the use of IVIg in gMG and may have been enhanced by the COVID-19 pandemic, which likely severely impacted patient care.

[6] Tindall RS, Phillips JT, Rollins JA, Wells L, Hall K. A clinical therapeutic trial of cyclosporine in myasthenia gravis. Ann N Y Acad Sci. 1993;681:539-551.
[7] Yoshikawa H, Kiuchi T, Saida T, Takamori M. Randomised, double-blind, placebo-controlled study of tacrolimus in myasthenia gravis [published correction appears in J Neurol Neurosurg Psychiatry. 2011 Oct;82(10):1180]. J Neurol Neurosurg Psychiatry. 2011;82(9):970-977.
[8] Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology. 2008;71(6):400-406
[9] Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016;87:419–425

Patients with AChR-Ab seronegative gMG have greater limitations on treatment options, as AChE inhibitors are known to have reduced efficacy in this population and new treatments like C5 or FcRn inhibitors are approved only for AChR-Ab seropositive patients.

Importantly, between the MG subgroups, the therapeutic regime can differ. Patients with MuSK antibodies tend to have more severe symptoms and generalized weakness, whereas treatment withdrawal in these patients can often lead to disease exacerbation. In addition, MuSK-MG patients can present with adverse effects when treated with pyridostigmine, an AChE inhibitor commonly used as a first-line treatment for MG, while there is little evidence to support the usefulness of thymectomy in these patients. On the other hand, they usually greatly benefit from PLEX, and they have a very good response to the administration of rituximab, possibly more pronounced than the other MG subgroups. AChR antibody positive patients who also have titin or RyR antibodies tend to have more severe disease, while in the case of early onset MG they are indicative of thymoma. The benefit of thymectomy is questionable in patients with seronegative MG, MuSK-MG and LRP4-MG since they usually lack the typical thymus pathology seen in AChR-MG. Especially in the case of Japanese patients, the presence of Kv1.4 antibodies has been associated with cardiac dysfunction and severe complications, so they should be monitored accordingly. The seronegative patients might have higher chance of ocular MG or better outcome than AChR-MG or MuSK-MG. It is, therefore, important to detect the autoantigen targeted in each patient for adopting the best treatment options.

Recently, a new class of treatment, neonatal Fc Receptor (FcRn) antagonists, has emerged as an add-on to standard therapy with a new mechanism of action targeting the underlying disease (e.g. Efgartigimod). FcRn has a specific role in IgG homeostasis by recycling IgG and rescuing it from lysosomal degradation.

2.2. About the product

Efgartigimod alfa is a human recombinant immunoglobulin 1(IgG1) derived Fc fragment produced in Chinese hamster ovary (CHO) by recombinant DNA technology. Efgartigimod alfa is engineered for increased affinity to the FcRn. Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies.

Pharmacological classification: Immunosuppressants, selective immunosuppressants, ATC code: L04AA58.

Vyvgart 20 mg/mL, concentrate for solution for intravenous infusion (also referred to as efgartigimod IV), was approved in the European Union on 10 August 2022 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-acetylcholine receptor antibody positive (EU/1/22/1674/001). The sought indication is the same for SC formulation.

The recommended dose is 1000 mg to be administered subcutaneously in cycles of once weekly injections for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient. If a scheduled injection is not possible, treatment may be administered up to 3 days before or after the scheduled time point.

Type of Application and aspects on development

The MAH did not seek for any scientific advice / protocol assistance from EMA during clinical development for gMG. A presubmission meeting with the (co)-rapporteur was held on 14 June 2022 to discuss this filing.

The MAH received feedback from FDA through three FDA type C meetings (04 Dec 2020, 08 Jun 2022, 12 Jul 2022) on various issues: quality (chemistry, manufacturing, and controls, nonclinical), clinical development of efgartigimod PH20 SC for the treatment of gMG including topics on self-administration, drug substance and

drug product testing strategy at release and stability, analytical comparability, shelf-life strategy, reference standard strategy, the selection and use of an NI margin, a fixed dose for all body weight groups, and total IgG as a pharmacodynamic (PD) marker for efficacy.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a solution for injection for subcutaneous (SC) administration containing 1000 mg (180 mg/mL) of efgartigimod alfa as active substance.

Other ingredients are: recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 (PS20), sodium chloride, sucrose and water for injections.

The finished product is available in a single-dose 6 mL type I glass vials with rubber stopper, aluminium seal and polypropylene flip-off cap.

2.3.2. Active Substance

2.3.2.1. General Information

Reference is made to Section 3.2.S.1 General Information for the efgartigimod 20 mg/mL active substance previously authorized with the finished product concentrate for solution for infusion.

2.3.2.2. Manufacture, process controls and characterisation

The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with good manufacturing practice (GMP). The efgartigimod 180 mg/mL active substance is manufactured by the same site responsible for the manufacture of the previously authorized 20 mg/mL active substance (Lonza Biologics Tuas Pte. Ltd., 35 Tuas South Avenue 6, Tuas 637377, Singapore).

Description of manufacturing process and process controls

The manufacturing process for efgartigimod 180 mg/mL active substance is based on a recombinant Chinese hamster ovary (CHO) cell line, containing the DNA sequence for the efgartigimod protein. The process strongly resembles a standard platform monoclonal antibody manufacturing process. In brief, cells from a vial of the working cell bank (WCB) are thawed and the cells are progressively expanded prior to inoculation of the production bioreactor. Upon completion of the cell culture, the production bioreactor contents are harvested by depth filtration to remove cells and cell debris and then filtered prior to further purification. Purification consists of chromatography steps, virus inactivation/reduction steps, and a concentration and diafiltration step. Following concentration and diafiltration (UF/DF) into the formulation buffer, the active substance undergoes excipient addition and is then bulk filtered and dispensed into the active substance containers.

Up to and including the last viral reduction step, the manufacturing process for efgartigimod 180 mg/mL active substance is identical to the process for the already authorized efgartigimod 20 mg/mL active substance, as implemented at Lonza Biologics, Tuas (Singapore). Reference is made to Section 3.2.S.2.2 Description of

Manufacturing Process and Controls for the efgartigimod 20 mg/mL active substance for information regarding the manufacturing process description and process controls up to and including the viral reduction filtration.

Flow diagrams have been included in the dossier indicating the raw materials used and the critical and non-critical process parameters (CCPs and non-CPPs) and quality attributes identified for each process step. In-process testing involves determination of adventitious agents at relevant stages, including bioburden and endotoxin levels and filter integrity testing.

Possibility of reprocessing is suggested in case of events related to specified process steps. No reprocessing is allowed due to non-compliant bioburden levels. Reprocessing of the abovementioned process steps will be qualified by means of prospective qualification protocols, describing the requirements for qualification of the reprocessing steps. This approach is endorsed.

Adequate resin reuse information was provided in the dossier for the multi-use resins. The lifetime will be verified at full scale under a concurrent validation protocol. This approach is found acceptable.

Overall, the efgartigimod 180 mg/mL active substance manufacturing process has been adequately described. The active substance manufacturing process is considered acceptable.

The container closure system for efgartigimod 180 mg/mL active substance is identical with the container closure system used for previously authorized efgartigimod 20 mg/mL active substance manufactured at Lonza Biologics, Slough (UK). The container closure system (CCS) is therefore found acceptable.

A risk assessment to evaluate potential extractables/leachables in the manufacturing process stream during the manufacture of efgartigimod 180 mg/mL active substance at Lonza Biologics, Tuas was performed to ensure compliance, safety and stability. All components that come in contact with the efgartigimod 180 mg/mL active substance during the manufacturing process at Lonza Biologics, Tuas (including CCS) were found to be compliant, within acceptable risk for leachables and pose no threat to the safety or quality of the product. Overall, the extractables/leachable risk assessment results are considered acceptable.

Control of materials

Reference is made to Section 3.2.S.2.3 Control of Materials for the previously authorized efgartigimod 20 mg/mL active substance manufactured at Lonza Biologics, Tuas for information on raw and starting materials used for cell culture stages, as well as for the harvest and purification steps. In summary, compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No raw materials of animal or human origin are used for the manufacture of efgartigimod 180 mg/mL active substance, except for the recombinant CHO production cell line.

For information on the source, history and generation of the cell substrate, as well as for master cell bank (MCB), working cell bank (WCB) and end of production cell bank (EOPC) generation, characterization, genetic stability and safety testing, cell line stability evaluation and generation of future WCB, reference is made to Section 3.2.S.2.3 Control of Materials for previously authorized efgartigimod 20 mg/mL active substance.

Control of critical steps and intermediates

Controls for all the critical steps have been established to ensure consistent quality of efgartigimod active substance produced by the commercial manufacturing process. The controls and limits were established based on historical knowledge (development and clinical data), process characterization studies and process performance qualification (PPQ) studies. Also, PPQ studies performed at Lonza Biologics, Tuas for the efgartigimod 20 mg/mL active substance were taken into account where relevant, due to the similarity of the

manufacturing process to the current efgartigimod 180 mg/mL active substance manufacturing process. This approach is considered acceptable as the process is identical up to and including the last virus reduction step. CPPs including acceptable range/limits are presented for the concentration and diafiltration, excipient addition and bulk filtration, dispensing and storage. The in-process controls (IPCs) in place are considered adequate to ensure that the active substance manufacturing process is in control and the corresponding acceptance criteria are considered appropriate. The microbial control strategy is considered adequate.

There are no process intermediates for the efgartigimod 180 mg/mL manufacturing process. Regarding the established in-process hold times for each manufacturing step up to and including the last virus reduction step, reference is made to Section 3.2.S.2.4 Controls of Critical Steps and Intermediates for the previously authorized efgartigimod 20 mg/mL active substance manufactured at Lonza Biologics, Tuas. For the UF/DF pool and formulated bulk, the validated in-process hold times are presented and are found acceptable.

Process validation

The commercial manufacturing process for efgartigimod 180 mg/mL active substance was validated at the commercial scale at Lonza Biologics, Tuas using 4 process performance qualification (PPQ) batches.

The process control strategy for the manufacture of efgartigimod 180 mg/mL active substance has been established based on and following a similar approach as for efgartigimod 20 mg/mL active substance. Acceptance criteria for process validation parameters were established based on Lonza platform knowledge, characterization studies and data from runs at the commercial scale. An interim risk assessment, to define and classify process inputs and outputs based on their criticality, was performed prior to running the PPQ campaign. CPPs and selected non-CPPs were monitored during the PPQ campaign to demonstrate that the manufacturing process could be executed within the established process parameter acceptable ranges and provided product which consistently met its pre-defined quality attributes. The critical quality attributes (CQA), quality attributes (QA) and performance attributes (PA) (outputs) were evaluated to assure the process performed as designed. Following completion of the PPQ campaign, the CQAs were reassessed and a final risk assessment was conducted to determine the final critical parameters and attributes and their corresponding acceptable ranges for the intended commercial manufacturing process and associated process control strategy.

The initial cell culture, harvest and downstream process validation was executed using batches derived from the same WCB using independent thaws and demonstrated acceptable process performance and batch to batch consistency. The purification process demonstrated consistent and effective removal of host cell-derived, cell culture media-derived and purification process-derived impurities. All PPQ batches complied with the applied QC release acceptance criteria.

In addition to the PPQ validation study, studies were conducted to support the product process validation. A few studies were not performed, as the manufacturing processes for efgartigimod 20 mg/mL active substance (Process LC2.2) and efgartigimod 180 mg/mL active substance (Process HC2.2) are identical up to and including the last virus reduction step, and the validation performed for efgartigimod 20 mg/mL active substance is applicable.

A summary of the shipping validation was provided at the required temperatures for the active substance transportation, demonstrating that the shipping container is qualified to maintain product storage temperature when subjected to thermal stress condition and to maintain the integrity of the active substance packaging following exaggerated physical stress.

In conclusion, the efgartigimod 180 mg/mL active substance manufacturing process conducted at Lonza Biologics, Tuas has been successfully validated through the PPQ studies performed at the respective site. A

continued process verification (CPV) program is in place in order to demonstrate an ongoing state of control over the lifecycle of the product.

Manufacturing process development

The manufacturing process for efgartigimod 180 mg/mL active substance (high concentration, HC) has been developed by Lonza Biologics, Tuas based on the manufacturing process for already authorized efgartigimod 20 mg/mL active substance (low concentration, LC).

To develop a new formulation and product presentation suitable for subcutaneous administration, different changes were introduced stepwise in the active substance manufacturing processes. The manufacturing processes for both the approved LC manufacturing process (LC2.2, for intravenous (IV) formulation of efgartigimod) and the intended commercial HC manufacturing process (HC2.2, for subcutaneous (SC) formulation of efgartigimod) are essentially identical, up to and including the virus reduction step. During the subsequent concentration and diafiltration step, the active substance is formulated in its final designated (IV or SC) formulation buffer. After the concentration and diafiltration step, polysorbate is added (polysorbate 80 for the IV formulation and polysorbate 20 for the SC formulation), followed by the final active substance filtration and filling step. The intended commercial manufacturing processes for efgartigimod 180 mg/mL active substance has the formulation corresponding to 180 mg/mL efgartigimod in L-histidine/ L-histidine HCl, sodium chloride, sucrose, L-methionine, PS20.

Two major process versions have been used thus far for the manufacture of efgartigimod 180 mg/mL active substance: the initial (non-commercial) Process HC1.0 at Lonza Biologics, Slough, UK (used for non-clinical safety and clinical Phase 1 studies, as well as Phase 3 clinical trials) and the intended commercial Process HC2.0 at Lonza Biologics, Tuas, Singapore (used for Phase 1 bridging studies and Phase 3 clinical trials).

The changes implemented have been adequately described and justified. Comparability across different manufacturing process versions, have been adequately demonstrated, based on comprehensive analytical comparability data packages, including release, in-process, extended characterization and stability data in accordance with ICH Q5E guideline. Therefore, it can be concluded that the changes made to the active substance manufacturing process did not have a significant influence on the quality of the product.

Characterisation

The elucidation of the primary structure conducted at protein, peptide and glycan level is described, as well as the higher-order structure, product-related variants/product heterogeneity, biological activity, active substance characteristics and characterization of efgartigimod variants, based on characterization studies with the current working reference standard formulated at 180 mg/mL. The characterization results were generated by side-by-side testing with the 20 mg/mL primary reference standard. All relevant structure-related quality attributes were addressed during characterization studies, using several orthogonal state-of-the-art analytical methods. Reference is also made to Section 3.2.S.3.1 Characterization for the already authorized efgartigimod 20 mg/mL active substance.

The results demonstrate that efgartigimod active substance has the expected structure of an IgG1 Fc fragment with increased binding specificity for the neonatal Fc receptor (FcRn) and that intrinsic structure and properties of the molecule remain intact, irrespective of the concentration and the formulation buffer. In summary, the characterization is considered appropriate for this type of molecule.

Impurities present in efgartigimod 180 mg/mL active substance are classified as product-related impurities and process-related impurities. Adequate information regarding the heterogeneity of the active substance has been presented by the applicant.

For the process-related impurities that may potentially be present in efgartigimod active substance, the applicant proposed appropriate control strategy and/or justification for not performing routine testing.

2.3.2.3. Specification

The efgartigimod 180 mg/mL active substance specification complies with the provisions of ICH Q6B and includes: testing for visual appearance, content, pH, identity, purity, potency, PS20 concentration, impurities and microbial impurities. Testing for absence of mycoplasma and adventitious viruses is performed as in-process controls on unprocessed bulk harvest, which is deemed acceptable. The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for the identity, safety, process-related impurities and PS20 which are tested only at release.

The proposed commercial specifications are set based on data from all active substance batches manufactured up to and including the PPQ batches. For some of the purity parameters, slightly wider limits for efgartigimod 180 mg/mL active substance compared to efgartigimod 20 mg/mL active substance are introduced, for which the applicant provided adequate justification. The acceptance criteria for potency testing and for size-related variants were also initially proposed by the applicant to be wider than the acceptance criteria for the currently approved efgartigimod 20 mg/ml active substance, however this was not found to be justified by PPQ data and, therefore, the applicant was requested to further tighten these limits and align with the approved acceptance limits for efgartigimod 20 mg/mL. The applicant was requested to also tighten the endotoxin acceptance limit and, although not aligned with the limit for efgartigimod 20 mg/mL active substance, the proposed acceptance criteria for endotoxin determination is acceptable.

In summary, the proposed tests panel and acceptance criteria for batch release/stability testing are considered adequate.

Analytical methods

The applicant has provided brief, but adequate descriptions have been provided for all compendial methods. Descriptions of all non-compendial methods have been provided, including principle, reagents, procedure (high-level), assay/system and sample suitability criteria, and evaluation and reporting of results.

Compendial methods used to test efgartigimod 180 mg/mL active substance are identical (except for the endotoxin method) to the methods involved in testing of efgartigimod 20 mg/mL active substance.

Non-compendial analytical procedures used to test efgartigimod 180 mg/mL active substance are also identical to the analytical procedures used for efgartigimod 20 mg/mL active substance, except (where applicable) for the initial sample preparation step. The method description for PS20 concentration is new and is found adequate.

Overall, the documentation provided for the validation of analytical procedures for efgartigimod 180 mg/mL active substance is considered comprehensive and the analytical methods are considered validated for their use.

Batch analysis

Batch analysis data of efgartigimod 180 mg/mL historical non-clinical and clinical batches (batches manufactured at Lonza Biologics, Tuas and 9 batches manufactured at Lonza Biologics, Slough), PPQ batches and post-PPQ batches are presented. All results comply with the specification in place at the time of testing and overall batch-to-batch consistency of the manufacturing process is demonstrated.

Reference materials

The quality of efgartigimod 180 mg/mL active substance is monitored by a two-tiered reference standard approach, using a primary reference standard (PRS) and a working reference standard (WRS). The current PRS and the current WRS are both established at 20 mg/mL and are identical with the ones used for the commercial large-scale process for the 20 mg/mL active substance. As the 20 mg/mL and 180 mg/mL active substance manufacturing processes only differ from the UF/DF step onwards, the PRS is considered suitable for efgartigimod 180 mg/mL. A new secondary WRS was established at 180 mg/mL, by aliquoting a portion of a clinical phase 3 efgartigimod batch that is formulated at 180 mg/mL and is representative of the commercial large-scale process for the 180 mg/mL active substance. This new WRS was characterized and adequately qualified by comparison against the current PRS.

In conclusion, the current PRSs and WRSs are considered properly qualified and fit for purpose. The reference standards are requalified annually according to standard operating procedures. A strategy for introducing new WRS has been outlined and is considered appropriate.

2.3.2.4. Stability

The applicant performed, in accordance with the ICH Q5C, a comprehensive series of stability studies for shelf-life determination and characterization of the stability profile of efgartigimod 180 mg/mL active substance. Based on these studies, the applicant proposed a shelf-life of 24 months for efgartigimod 180 mg/mL active substance, at the intended storage condition.

The stability studies included primary PPQ batches (manufactured at Lonza Biologics, Tuas) and supportive stability batches (manufactured at the same site). Based on the comprehensive comparability data, the supportive batches are considered representative for the final commercial active substance and the stability data generated with these batches can be used for shelf-life determination of the efgartigimod 180 mg/mL active substance. Furthermore, stability data from additional active substance batches manufactured according to the historical manufacturing processes have been presented. As these batches used a different final formulation, the results are only included for information.

The stability studies were conducted under long-term storage condition, accelerated storage conditions and stressed storage conditions.

Long-term stability data are presented for up to 24 months for the primary PPQ batches. Long-term stability data are presented for up to 24 months for the supportive batches. The stability data shows that the tested CQAs of the active substance were stable and within the shelf-life acceptance criteria and no stability trends were seen in the quality of the efgartigimod 180 mg/mL active substance when stored at long-term conditions.

The stress temperature stability study results demonstrate the stability-indicating properties of the test methods. Forced degradation studies, together with the accelerated and stress temperature studies, showed the main degradation pathways of efgartigimod 180 mg/mL active substance. The applicant also evaluated the effect of freeze/thaw cycles on the active substance stability with 1 supportive batch. Comparable results for the tested parameters were obtained for the samples subjected to freeze/thaw cycles at small scale and at scale containers and stored for 9 months. Since the applicant demonstrated comparability between active substance manufactured throughout process development, the supportive batch is considered representative and the applicant's conclusion that there is no marked impact on the product quality of efgartigimod 180 mg/mL active substance for to up to 5 freeze/thaw cycles can be accepted.

In conclusion, the stability results indicate that the efgartigimod 180 mg/mL active substance is sufficiently stable over the proposed shelf-life of 24 months when stored in the proposed container.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and Pharmaceutical Development

The finished product (efgartigimod PH20) is presented as a sterile, preservative-free, clear to opalescent, yellowish solution for subcutaneous injection. The product contains 1000 mg of efgartigimod active substance at a concentration of 180 mg/mL and 11200 U of recombinant human hyaluronidase PH20 (rHuPH20) at a concentration of 2000 U/mL, in a L-histidine/L-histidine HCl, sodium chloride, sucrose, L-methionine, PS20 buffer.

The excipients are added during active substance manufacturing, except for rHuPH20 which is added during manufacturing of the finished product. There is no overage in the efgartigimod finished product. An 8% overfill is applied up to a target fill volume of 6.7 mL necessary to ensure withdrawal of at least 6.2 mL that allow for the delivery of the required 5.6 mL volume.

Efgartigimod finished product contains well-known pharmaceuticals ingredients and their quality is compliant with Ph. Eur. standards, with the exception of rHuPH20 which is tested as per in-house specification. No novel excipients or excipients of human or animal origin are used in the finished product composition. Compatibility of the active substance with the excipients is considered demonstrated based on both active substance and finished product stability data.

The rHuPH20 specification for release and stability are identical, except for tests for identity, impurities and safety tests which are only performed at release. A summary of the analytical procedures and validations hereof are included in the dossier. Justification of the release and stability acceptance criterion for each individual test attribute is provided and summarized. In summary, the rHuPH20 specifications, including acceptance criteria and analytical procedures, are considered acceptable.

During the assessment, a Major Objection was raised for the insufficient information provided for the rHuPH20 excipient with regards to description of the manufacturing process, control of materials, process validation, characterization of rHuPH20, impurity testing, stability and viral safety assessment. In its response, the applicant clarified that the rHuPH20 used for efgartigimod PH20 finished product is of the same quality and manufactured by the same manufacturer as the rHuPH20 excipient currently used in several already EU-marketed products. In addition, a statement confirming a quality agreement between rHuPH20 manufacturer and the manufacturer of the efgartigimod PH20 finished product has been provided, ensuring that the finished product manufacturer will be notified of any rHuPH20 manufacturing process changes that might affect the quality of the final product. This approach is endorsed, and the major objection is considered resolved.

Container closure system

Efgartigimod PH20 finished product is filled into 6 mL glass vials (Ph. Eur. type I). The glass vial is stoppered with a rubber stopper and closed using an aluminium crimp seal equipped with a polypropylene flip-off cap. The materials for the primary packaging of the finished product are in line with Ph. Eur. requirements. The CCS is suitable for the finished product as demonstrated by the long-term stability data and container closure integrity (CCI) under the applied stoppering and capping conditions has been successfully demonstrated through dye ingress testing.

Extractables and leachables studies have been performed on the container closure components. Considering that the proposed finished product presentation includes the same container/closure materials specifications and only a slightly different formulation, the target compound selection for the leachable study was based on the extractable study performed for the IV formulation. A leachable screening study is ongoing to identify and quantify leachable compounds in batches of efgartigimod PH20 finished product. The results of the extractables and ongoing leachables studies (up to 3 months of long-term and accelerated studies) performed on the commercial primary packaging (vial and stopper) configuration for efgartigimod PH20 finished product demonstrate that the selected CCS is suitable for use for the finished product. The Applicant has confirmed that leachables studies will be continued until 60 months at long-term conditions and until 12 months at accelerated conditions. This approach is endorsed.

In-use compatibility

In order to deliver the finished product, the solution needs to be extracted from the vial using a syringe-needle combination and SC administered through a winged infusion set. An in-use compatibility/short-term stability study was performed to demonstrate that the subcutaneous administration procedure does not impact efgartigimod PH20 product quality attributes and to demonstrate the compatibility of efgartigimod PH20 solution for subcutaneous injection with different auxiliary material combinations. No change in physico-chemical quality attributes was observed over the monitored time period of 30 hours (24 hours at 5°C plus 6 hours at 30°C) for the finished product in syringe prior to administration. A microbial hold study was performed with selected challenge organisms on the finished product in syringes to simulate potential microbial contamination that may occur during the preparation and storage of syringes, prior to SC administration. No microbial growth was observed in spiked syringes containing efgartigimod PH20 finished product. The results support the hold of the efgartigimod PH20 finished product in syringe, following dose preparation, for up to 24 hours at +2°C to +8°C and for up to 2 hours (cumulatively) at ambient temperature.

Pharmaceutical development

The pharmaceutical development approach was based on the following elements: definition of a Quality Target Product Profile (QTPP), identification of potential Critical Quality Attributes (CQAs) of the finished product, selection of the appropriate manufacturing process, determination of the CQAs of the active substance, selection of the excipients and the container closure system, and definition of the quality control strategy. The QTPP includes: intended indication, mechanism of action as well as the molecule critical features impacting the mechanism of action, dosage form, mode of administration, dose, concentration, strength, container closure system, shelf-life stability and compatibility with the application devices and the manufacturing process, as well as the finished product quality requirements (compliance with the requirement for parenteral preparations).

Based on the QTPP, CQAs were defined. CQAs have initially been determined for efgartigimod 20 mg/mL active substance and the corresponding efgartigimod IV finished product. As the manufacturing process for efgartigimod 180 mg/mL active substance is identical to the process for the efgartigimod 20 mg/mL active substance, up to and including the last viral reduction step, a large part of the CQA assessment for efgartigimod 20 mg/mL are also applicable for efgartigimod 180 mg/mL. These elements were integrated in the CQA assessment performed prior to PPQ for efgartigimod 180 mg/mL active substance and efgartigimod PH20 solution for SC injection. The assessment was based on a review of all available historical quality, non-clinical and clinical data linked to efgartigimod product development. The proposed approach is considered acceptable.

The formulation development of a SC administered efgartigimod finished product covered 6 different high concentration formulations for SC administration that were developed and used throughout non-clinical and

clinical development. The formulations differ in efgartigimod concentration, rHuPH20 concentration and formulation buffer. In summary, the formulation development is considered adequately described.

The finished product manufacturing process is a standard process consisting of mixing rHuPH20 with efgartigimod active substance followed by sterile filtration, aseptic filling, stoppering and capping. No finished product process development activities were performed, but product presentation changed over time and thus the fill volume and vials used. Two manufacturing sites have been used during development of the finished product manufacture. The manufacturing processes are comparable and comparability of efgartigimod PH20 finished product manufactured at both sites has been demonstrated. The majority of the clinical development activities for the efgartigimod PH20 finished product took place at the intended commercial manufacturing site, in accordance with the commercial manufacturing process and only 1 clinical batch was manufactured at the other manufacturing site.

The development of the process control strategy was also presented by the applicant. A risk assessment was conducted prior and post-PPQ manufacture using a Failure Modes and Effects Analysis (FMEA) method, which evaluated the potential effects that various process parameters may have on product quality attributes and manufacturing process performance. Based on the outcome of the risk assessment exercise, a final classification of process parameters (as either CPP or non-CPP) for the PPQ campaign was performed. Overall, the proposed sets of process and release controls are reasonable.

In conclusion, sufficient details regarding the finished product process development were presented by the applicant.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

The efgartigimod PH20 finished product is manufactured, filled, packaged, inspected and tested in accordance with GMP. The efgartigimod PH20 finished product batch formula has been provided for the intended commercial batch size range.

Efgartigimod PH20 finished product manufacturing process is considered standard and consists of thawing of the active substance, thawing of the rHuPH20 bulk enzyme, pooling and mixing of the active substance with rHuPH20 bulk enzyme, bioburden reduction filtration, sterile filtration, aseptic filling, stoppering and capping operations, visual inspection, sampling for analytical testing, vial labelling, secondary packaging, serialization and storage. All process steps are performed at room temperature (15°C to 25°C), except thawing of the rHuPH20 bulk enzyme which is performed at 2°C to 8ºC.

There are no reprocessing steps and no intermediates in the efgartigimod PH20 finished product manufacturing process. The process controls associated with the efgartigimod PH20 finished product manufacturing process are categorized as process parameters or as in-process controls. For each manufacturing step, a summary of the established process controls, their criticality (i.e. CPP or non-CPP), hold times, test methods and acceptance criteria are presented. The critical steps that may have a direct impact on the CQAs of the finished product are also listed, together with appropriate controls.

Overall, the manufacturing process and the equipment used is considered adequately described.

Process validation and/or evaluation

The PPQ was performed with commercial scale batches. The process validation included hold/processing time challenges, homogeneity testing, consistency of the aseptic operation testing, results of routine in-process control testing, visual inspection, release testing. All IPCs and release data of the PPQ batches comply with the predefined acceptance criteria and the release specification, including the batches manufactured using the maximum hold and processing times.

An overview and a summary of the performance qualification for the key equipment used for manufacture of efgartigimod finished product is presented. Aseptic manufacturing is regularly confirmed by media fills (at least twice a year) and results of the most recent media fills show that the pre-defined acceptance criteria are met. The aseptic filling process, representative of the finished product manufacturing process, is documented to be validated for a maximum filling duration of 24 hours. The validation of the sterile filtration demonstrated that the process consistently provided a sterile solution and that the risk for patients treated with efgartigimod finished product due to extractables from the filter devices used for filtering the finished product is negligible.

Shipping studies were performed, and results confirm that the shipping containers are able to maintain the integrity of the efgartigimod product package following exaggerated physical stress.

Continued process verification (CPV) is conducted during the entire life cycle of the product.

In conclusion, the efgartigimod PH20 finished product manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.3.3.3. Product specification, analytical procedures, batch analysis

The proposed release specification for the efgartigimod PH20 finished product includes tests for visual appearance (colour, clarity and visible particles), osmolality, extractable volume, sub-visible particles, protein concentration, pH, identity, identity rHuPH20, potency, purity, PS20 concentration, rHUPH20 activity and safety. The same parameters are tested during shelf-life, except for extractable volume, identity and identity rHuPH20. No widening of the finished product release criteria was considered for stability studies.

Most of the test parameters and acceptance criteria proposed for the control of the finished product are identical with the tests and acceptance criteria applied for the 180 mg/mL active substance. As for the active substance, acceptance limits for potency, purity and endotoxin have been tightened upon request to be aligned with acceptance limits approved for efgartigimod IV finished product, except for one purity parameter. The proposed limit is supported by clinical data and is considered acceptable. In addition, the endotoxin limit is slightly higher in case of the efgartigimod PH20 finished product compared to the acceptance criteria applied for the 180 mg/mL active substance, which is justified by the need to account for addition of recombinant rHuPH20 during the finished product manufacture.

No new impurities/degradation products are formed during the efgartigimod PH20 finished product manufacturing process compared to the active substance.

Elemental impurities were evaluated according to ICH Q3D guideline. Based on the risk assessment for the efgartigimod active substance, excipients, rHuPH20 bulk enzyme, container closure system and the results of elemental impurities analysis on representative finished product batches, it is concluded that the overall risk of a potential release of elemental impurities into the efgartigimod PH20 finished product is low. Therefore, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. This conclusion is supported.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Overall, the parameters included in the efgartigimod PH20 finished product specification are found adequate to control the quality of the product at release and shelf-life. Justification of specification is based on historical data, data on process qualification batches and post-PPQ batches.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. The methods are the same as those used to test efgartigimod 180 mg/mL active substance, except for tests for osmolality, extractable volume, visible and sub-visible particles, rHuPH20 identity and enzyme activity and safety, which are product-specific assays. Tests for appearance, protein concentration, pH, identity, potency, purity and PS20 concentration are also performed on the active substance.

Batch analysis

Batch analysis data are presented for PPQ and post-PPQ batches. The batch data presented complies with the finished product specification and demonstrates consistency of the manufacturing process. In addition, supportive historical batch data has been provided.

Reference materials

The efgartigimod reference standard used for analytical testing of efgartigimod PH20 finished product is the same as used for analytical testing of efgartigimod active substance. Reference is made to the active substance section on Reference materials.

For the rHuPH20 standard (Assay Reference Standard - ARS), used for analytical testing of efgartigimod PH20 finished product, a two-tiered reference standard strategy consisting of an established PRS and a WRS has been implemented. The current ARS was established as both PRS and WRS. Upon depletion of the working reference standard aliquots, a replacement working reference standard will be calibrated and qualified against the respective established primary reference standard. The current ARS was generated from a rHuPH20 BE (bulk enzyme) batch that met all release specifications, as well as tighter selection acceptance criteria for protein concentration and specific activity (potency). Additional characterization testing was performed. The characterization assays, acceptance criteria and results obtained for rHuPH20 BE source batch are specified. In summary, the current primary and initial working ARS lot is considered qualified for use in the rHuPH20 enzyme activity assay. The reference standard is re-evaluated on an annual basis in accordance with an established quality system.

2.3.3.4. Stability of the product

The applicant is proposing a shelf-life of 18 months at 5°C ± 3°C for efgartigimod PH20 finished product. Stability studies were performed on 3 primary PPQ batches, supportive batches and additional batches,

following storage at 5°C ± 3°C (long-term storage condition), 25°C ± 2°C/60 ± 5% relative humidity (accelerated storage condition) and 40°C ± 2°C/75 ± 5% relative humidity (stressed storage condition). The primary stability batches were manufactured at the proposed commercial site, using PPQ active substance batches. Supportive batches were manufactured at both clinical manufacturing sites. Based on both the active substance and finished product comparability packages, these non-PPQ batches are considered representative for the final commercial finished product and the stability data can be considered supportive for shelf-life determination. The additional finished product batches have not been considered for shelf-life determination since they had a different final formulation and/or since the active substance was manufactured at Lonza Biologics, Slough and not at the commercial site (Lonza Biologics, Tuas). Therefore, stability data for these batches is presented for information only.

The stability testing program was performed in accordance with the ICH guideline Q5C, using adequate test intervals, stability-indicating methods and representative CCS. Available long-term stability data from primary batches showed that the tested CQAs of the finished product were stable and within the shelf-life acceptance criteria over an 18 months time period under long-term storage condition. This was also supported by either 18 or 24 months of stability data from supportive batches, which demonstrated a comparable and stable profile of the finished product within the tested time period.

Based on the data generated from the accelerated and stress studies, the primary degradation pathways of the efgartigimod PH20 finished product were identified and the methods used were demonstrated to be stability-indicating. The photosensitivity of the finished product was performed on a PPQ batch placed into a photostability study performed in accordance with the ICH Q1B guideline. The photostability data indicate that the finished product complies with the current acceptance criteria when kept in the proposed secondary packaging configuration. Based on the results obtained for the fully exposed (primary packed) vials, it can be concluded that efgartigimod vials must be stored in their outer cartons.

In summary, based on available stability data, the shelf-life of efgartigimod PH20 finished product of 18 months and storage conditions as stated in the SmPC (*Store in a refrigerator (2°C - 8°C)*. *Do not freeze. Store in the original package in order to protect from light*) are acceptable.

In addition, for the unopened vials, the following storage condition is proposed in the SmPC and is considered justified by the in-use compatibility studies: *If needed, unopened vials may be stored at room temperature (up to 30 °C) for up to 3 days. After storage at room temperature, unopened vials may be returned to the refrigerator. If stored out of and then returned to refrigeration, the total combined time out of refrigeration should not exceed 3 days. From a microbial point of view, unless the method of preparation of the syringe precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.*

2.3.3.5. Adventitious agents

Non-viral adventitious agents

No animal or human-derived raw materials were used during generation of the efgartigimod production cell line or establishment and storage of MCBs and WCBs or during the manufacturing process of the efgartigimod active substance. Reference is made to Section 3.2.S.2.3 Control of Materials for previously authorized efgartigimod 20 mg/mL active substance.

During routine manufacture, appropriate measures are in place for controlling the risk of contamination with non-viral adventitious agents, including testing and control of raw materials, testing of EOPC at the limit of *in*

vitro cell age (LIVCA), the facilities and equipment used, filtration of process solutions through sterilizing grade filters prior to use and performing in-process controls for bioburden, endotoxin and mycoplasma/fungi. In addition, the efgartigimod 180 mg/mL active substance and the efgartigimod PH20 finished product are tested for endotoxin level and absence of fungi and bacteria at release and during shelf-life, using compendial methods (Ph. Eur.).

Based on the information provided, the risk of BSE/TSE (Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy) contamination of efgartigimod PH20 finished product during manufacturing is considered negligible.

Viral adventitious agents

The purification process used at Lonza Biologics, Tuas for the manufacture of 180 mg/mL active substance is the same as the process for the 20 mg/mL active substance, up to and including the last virus reduction step. Therefore, the viral clearance studies described for the efgartigimod IV finished product are also applicable to the efgartigimod 180 mg/mL active substance and SC finished product. Therefore, reference is made to Sections 3.2.A.2 Adventitious Agents Safety Evaluation and 3.2.R.2 Viral Safety Package for the previously authorized efgartigimod IV finished product.

During the efgartigimod manufacturing process, samples are taken to monitor and demonstrate control of adventitious viral agents in accordance with ICH Q5A guideline. In-process controls are performed on unprocessed active substance bulk samples taken on the day of harvest. No adventitious viral agents have been detected in the unprocessed bulk for any batches of efgartigimod 180 mg/mL active substance.

The cumulative reduction factors for the 20 mg/mL process at Lonza Biologics, Tuas have been used to determine the retrovirus-like particles per dose and safety margin data for the 180 mg/mL active substance. The results demonstrate a low and acceptable risk.

The viral safety data provided by the applicant for raw materials of biological origin, cell bank testing, bulk harvest testing, virus clearance validation studies and retroviral risk assessment is considered acceptable.

rHuPH20

An adventitious agents safety evaluation for the rHuPH20 bulk enzyme is also presented by the applicant. The BSE/TSE risk is considered negligible, based on that fact that no animal or human-derived materials are used during generation of the production cell line or establishment and storage of MCBs and WCBs or the manufacturing process of rHuPH20 excipient, except for the media used for the manufacture of a process aid used to convert the insulin to the active form that contains two bovine derived components, amicase and lactose. As these components are derived from healthy animals and are exposed to a thermal treatment, they comply with the "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents by a human or veterinary medicinal products" (EMA/410/01 rev. 3) and pose no risk to the patient safety. In addition, this process aid is removed in the subsequent purification and isolation steps in the insulin manufacturing process.

Moreover, the cell banks and manufacturing process for the excipient rHuPH20 enzyme are tested for presence of viruses. The process contains orthogonal viral clearance steps which were challenged with 4 model viruses. A viral safety risk assessment was performed demonstrating robust viral clearance and provides assurance of viral safety for the excipient rHuPH20 enzyme.

Overall, the information presented for the BSE/TSE and viral safety evaluation for rHuPH20 is considered acceptable.

2.3.3.6. GMO

Not applicable.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

A Major Objection was raised during the assessment for the insufficient information submitted for the rHuPH20 non-compendial biological excipient, which has been adequately addressed by the applicant by the end of the procedure.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

The mode of action was already well described in the initial marketing authorisation application (MAA) for IV administration. In the present extension application, an additional study exploring the effects of efgartigimod on the PD drug interactions of efgartigimod with IVIg and a tracer antibody, in Tg32 mice. No specific pharmacology studies were performed using the SC route of administration.

In brief, the mode of action represents a rational therapeutic approach in autoimmune diseases mediated by IgG autoantibodies. The proposed indication for efgartigimod PH20 SC is the treatment of adult patients with gMG. Nonclinical pharmacology studies have shown that efgartigimod binds to FcRn, reduces concentrations of IgG in the circulation including pathogenic autoantibodies and reduces signs of disease in animal models. The mode of action of efgartigimod (saturation of FcRn and linked enhanced clearance of pathogenic IgG) avoids

suppression of T- and B-cell activity and preserves IgM and IgA levels because homeostasis of those Ig classes does not rely on FcRn. In addition, efgartigimod does not affect serum albumin concentrations, because it does not interfere with the albumin-FcRn interaction.

2.4.2.1. Pharmacodynamic drug interactions

A new PD drug interaction study was submitted, which investigated the effect of IVIg and efgartigimod treatment. It was shown that efgartigimod levels following an IV dose of 20 mg/kg were not influenced by IVIg after coadministration regardless of the treatment scheme. In reverse, efgartigimod reduced but did not eliminate levels of IVIg measured as total IgG.

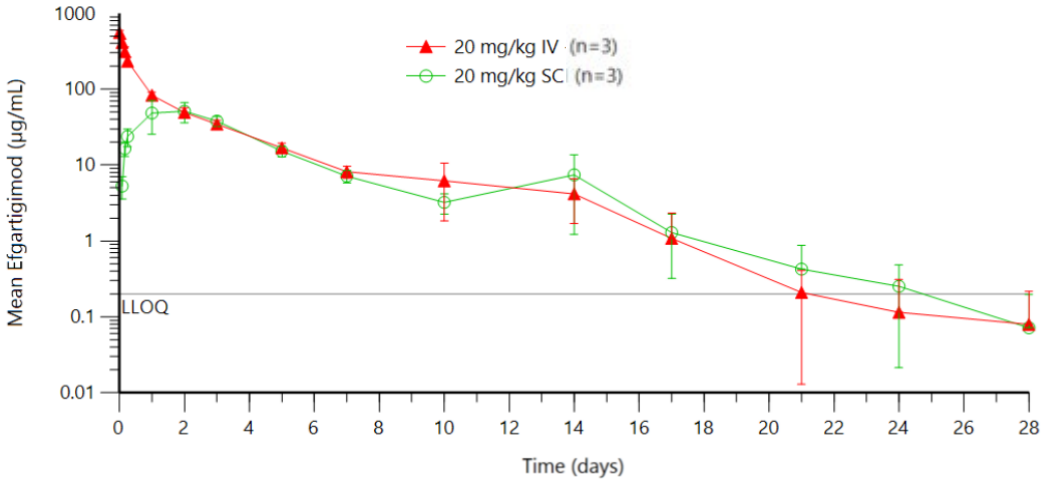
2.4.3. Pharmacokinetics

Only two studies in cynomolgus monkeys were performed with SC administration of efgartigimod, one single dose pharmacokinetics (PK)/PD study, and a 12-week repeat dose toxicity bridging study. Furthermore, pharmacokinetics was (re)calculated using a noncompartmental PK/PD model.

Pharmacokinetic Evaluation After Single Dose of Efgartigimod SC in Cynomolgus Monkey (Study No ARGX-NC-092)

The PK and PD effects after a single SC dose of efgartigimod 20 mg/kg (without recombinant human hyaluronidase PH20 (rHuPH20)) were evaluated. Cynomolgus monkeys were treated with a single 20 mg/kg SC injection or a single 20 mg/kg IV infusion of efgartigimod. After SC administration, peak concentrations were reached after 24 to 48 hours and were approximately 10-fold lower as compared to after IV administration. Thereafter, serum concentrations declined and were comparable to after IV administration (Figure 1).

Figure 1: Mean (±SD) Serum concentration-time profiles of Efgartigimod after a single IV bolus or SC injection of 20 mg/kg in Cynomolgus Monkeys



IV=intravenous; LLOQ=lower limit of quantification; n=number of animals; SC=subcutaneous; SD=Standard deviation.

Based on the shape of the PK profile, a dominant or effective elimination half-life ($t_{½,eff}$) and terminal elimination half-life ($t_{½,z}$) were apparent. After SC injection, a $t_{½,eff}$ of 46.2 hours was estimated based on the sampling time points from 24 hours up to 168 hours or 240 hours postdose. The $t_{½,z}$ of 160 hours was estimated based on the terminal portion of the curve. $AUC_{0\text{-}168h}$ represented approximately 80% of area under the concentration-

time curve from time zero to infinity ($AUC_{0\text{-}inf}$) supporting the relatively small contribution of the terminal elimination phase to the total exposure. Therefore, $t_{½,eff}$ is considered to be more relevant for the elimination and accumulation of efgartigimod. Similar observations were made as after IV administration. Compared to after efgartigimod IV 20 mg/kg, the bioavailability of efgartigimod SC 20 mg/kg (without rHuPH20) was estimated to be approximately 50% (Table 1).

Table 1: summary of efgartigimod PK parameters after a single IV bolus or SC injection of 20mg/kg in Cynomolgus Monkeys

Species	**Cynomolgus monkey**	
Dose (mg/kg)	**20 IV**	**20 SC (without rHuPH20)**
No. per group/sex	**3M**	**3M**
C_{max} (µg/mL)	554±37.6	53.2±18.7
t_{max} (h)	0.08 (0.08-0.08)	48 (24-48)
$AUC_{0\text{-}168h}$ (µg.h/mL)	9124±1018	4676±1113
$AUC_{0\text{-}last}$ (µg.h/mL)	10 327±1693	5868±1652
$AUC_{0\text{-}inf}$ (µg.h/mL)	10 501±1614	5969±1634
CL(/F) (mL/h/kg)	1.93±0.284	3.53 ± 0.991
$t_{½,eff}$ (h)	44.7±1.96	46.2±5.88
$t_{½,z}$ (h)	96.9±28.8	160±120
V_{ss} (mL/kg)	138±8.79	NA

$AUC_{0\text{-}xh}$=area under the concentration-time curve (AUC) from time zero to x hours postdose; $AUC_{0\text{-}inf}$=AUC from time zero to infinity; $AUC_{0\text{-}last}$=AUC from time 0 to the last quantifiable concentration; CL(/F)=(apparent) systemic clearance; C_{max}=maximum observed concentration; IV=intravenous; M=male; NA=not assessable; no.=number; PK=pharmacokinetics; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; SD=standard deviation; $t_{½,eff}$=effective elimination half-life; $t_{½,z}$=terminal elimination half-life; t_{max}=time of Cmax; Vss=volume of distribution at steady-state Note: Values are arithmetic means (±SD) except median (min-max) for t_{max}.

Pharmacokinetic Evaluation After 12-Weekly SC Injections in Male and Female Cynomolgus Monkey

In this GLP-compliant 12-week repeat-dose toxicity study with weekly SC doses of efgartigimod 30 and 100 mg/kg comixed with 2000 U/mL rHuPH20 and efgartigimod 100 mg/kg without rHuPH20 in cynomolgus monkey.

Serum samples were taken predose and at 8, 24, 48, 72, and 144 hours postdose after the first and the last dose. At all other dosing days, a predose and a 24-hour post dose sample were taken.

After SC administration of efgartigimod 30 or 100 mg/kg comixed with 2000 U/mL rHuPH20, the PK evaluation revealed a dose-related increase in C_{max} and $AUC_{0\text{-}144h}$ after the first and last dose. The dose proportion factor ranged from 0.78 to 1.03. No sex-specific differences were observed and no substantial accumulation was noted.

rHuPH20 appeared to have minimal effect on the multiple dose PK of efgartigimod. After the last SC dose of efgartigimod 100 mg/kg comixed with 2000 U/mL rHuPH20, in both males and females, mean time of maximum observed concentration (t_{max}) was reached between 8 to 24 hours. Maximum observed concentration (C_{max}) and $AUC_{0\text{-}144h}$ were 585/402 µg/mL and 34 030/22 182 µg.h/mL in males/females, respectively. After the last SC dose of efgartigimod 100 mg/kg without rHuPH20, in both males and females, mean t_{max} was reached between 8 to 16 hours. C_{max} and $AUC_{0\text{-}144h}$ were 377/378 µg/mL and 25 143/19 973 µg.h/mL in males/females, respectively.

Table 2: TK parameters of Efgartigimod after the first (Days 1 to 7) and the last (13th) SC administration (Day 85 to 91) of Efgartigimod with or without rHuPH20 in cynomolgus monkey (12-Week study)

Efgartigimod dose (mg/kg) q7d	**30[a]**	**100[a]**	**100**	**30[a]**	**100[a]**	**100**
Gender and number per group	**3+2M**	**3+2M**	**3+2M**	**3+2F**	**3+2F**	**3+2F**
Days 1 to 7 (n=5/sex/group)						
C_{max} (µg/mL)	215±33.9	435±107	259±44.7	201±26.0	461±158	234±94.7
t_{max} (h)	8.0±0.0	11.2±7.2	38.4±13.1	8.0±0.0	11.2±7.2	43.2±10.7
$AUC_{0\text{-}tlast}$ (µg*h/mL)	8551 ±1761	22 357 ± 2995	19 270 ± 3396	8328 ± 1061	21 741 ±2898	17 498±4825
$AUC_{0\text{-}tlast}$/dose (µg*h/mL)	285 ± 58.7	224 ± 30.0	193 ± 34.0	278± 35.4	217±29.0	175±48.3
DPF	NA	0.78	0.68[b]	NA	0.78	0.63[b]
Days 85 to 91 (n = 2/sex/group)						
C_{max} (µg/mL)	534	585	377	208	402	378
t_{max} (h)	24.0	16.0	8.0	16.0	8.0	16.0
$AUC_{0\text{-}tlast}$ (µg*h/mL)	12 011	34 030	25 143	6488	22 182	19 973
$AUC_{0\text{-}tlast}$/dose (µg*h/mL)	400	340	251	216	222	200
DPF	NA	0.85	0.63[b]	NA	1.03	0.92[b]
R	1.40	1.52	1.30	0.78	1.02	1.14

$AUC_{0\text{-}tlast}$= AUC from time 0 to the last quantifiable time-point; C_{max}=maximum observed concentration; DPF=dose proportion factor; F=female; M=male; n=number of animals, subjects or samples; NA=not applicable; q7d=once every 7 days (once weekly); R=accumulation factor; rHuPH20=recombinant human hyaluronidase PH20; SD=standard deviation, TK=toxicokinetics; t_{max}=time of C_{max}
Notes: Values reported are arithmetic mean ±SD. No SD presented in case n equals 2.
a Comixed with 2000 U/mL rHuPH20.
b DPF calculated relative to 30 mg/kg efgartigimod SC comixed with rHuPH20

In summary, the following important PK characteristics of efgartigimod as assessed after IV administration were confirmed after SC administration: dose-proportional increase in C_{max} and AUC with comparable DPFs for both sexes and a lack of accumulation over time was corroborated.

A translational PK/PD model (study 20 021 TPKPD) was developed to describe the efgartigimod serum PK profile (without rHuPH20) and its effect on total IgG concentrations through pH 7.4 FcRn target binding in healthy subjects, cynomolgus monkeys (IV/SC), rabbits (IV), rats (IV) and mice (IV). In the model, reduction of total IgG was linked to receptor occupancy after IV administration, which could subsequently be used to postulate serum concentrations after SC administration, assuming linear PK behaviour and a bioavailability of 50% after SC administration. Lower receptor occupancy (RO) (91.4%) after SC administration in cynomolgus monkeys is predicted based on the model compared to 97% RO in cynomolgus monkeys after IV administration of 100 mg/kg/day.

2.4.4. Toxicology

2.4.4.1. Repeat dose toxicity

The 26-week study, described in the nonclinical overview as the most relevant for assessing toxicity of efgartigimod was already submitted and evaluated in the initial MAA, and will not be presented in detail in this round. The No Observed Adverse Effect Level (NOAEL) from this study was 100 mg/kg once every 7 days / weekly (q7d), and this was used as the high dose level in the bridging study performed with SC administration of efgartigimod.

A 12-week bridging study, where cynomolgus monkeys were administered efgartigimod SC with or without the absorption enhancer rHuPH20 administered q7d was performed. This study is presented and discussed in the current assessment. No significant new toxicity was observed compared to the previously performed studies where the intravenous route of administration was used. Local signs of intolerance were noted in form of a swelling in the animals treated with 100 mg efgartigimod /kg b.w. with 2000 U/mL rHuPH20 and in form of haematoma, swelling and/or oedema in the animals treated with 100 mg efgartigimod /kg b.w. alone. The NOAEL was considered to be 100 mg/kg efgartigimod with or without 2000 U/mL rHuPH20.

No clinical pathology assessment examining the expected pharmacological effect of reduced IgGs was included. This would have been relevant, especially considering that rHuPH20 was not part of the formulation in the PK/PD study (ARGX-NC-092) comparing PD and PK of IV or SC administered efgartigimod. However, as the TK measurements show systemic exposure of efgartigimod, the lack of any indication on PD effect can be considered acceptable.

2.4.4.2. Toxicokinetic data

The C_{max}-levels and AUC-areas for efgartigimod revealed a roughly linear dose-related exposure of the animals to efgartigimod on test days 1 to 7 (i.e. 144 hours after the first administration), and 85 to 91 (i.e. 144 hours after the last administration). No sex-specific differences were noted. No accumulation with time was noted. The addition of 2000 U/mL rHuPH20 gave rise to an apparent higher C_{max} and AUC, compared to SC formulation without this addition.

The exposure margins calculated using the AUC and C_{max} form the 26-week IV study in cynomolgus monkeys, gave rise to exposure multiples of 5- and 52-fold respectively, when compared to clinical exposure following subcutaneously administered efgartigimod 1000 mg. These are considered sufficient and are reflected in the SmPC section 5.3.

2.4.4.3. Local tolerance

A stand-alone local tolerance study in rabbits showed no specific test item related differences between Vyvgart SC formulation or vehicle administered alone (rHuPH20). Subcutaneously 1.0 ml was injected, and intramuscularly 0.25 ml was administered.

2.4.4.4. Other toxicity studies

Antigenicity

A high number of anti-drug antibody (ADA's) were observed following SC administration of efgartigimod with or without rHuPH20. The exposure of the animals did not appear to be affected.

Table 3: Summary of Number of Animals with positive ADA responses in Cynomolgus Monkeys (12-week study)

Number of ADA positive animals /total number of animals in the group								
Dose (mg/kg q7d)	0		30 efgartigimod SC comixed with rHuPH20		100 efgartigimod SC comixed with rHuPH20		100 efgartigimod SC	
	M	F	M	F	M	F	M	F
Treatment period (5 animals/sex/group)								
Day 1 to Day 85	NA	NA	5/5	5/5	4/5	4/5	5/5	4/5

ADA=Anti-Drug antibody; SC=subcutaneous; F=Female; M=Male; q7d=once weekly; NA=Not analyzed.
Note No ADA samples were taken during the recovery period. 2000 U/ml rHuPH20 was used.

Immunotoxicity

A transitory reduction in anti-KLH specific IgG antibody response as well as in total IgG titers were observed in animals administered 100 mg/kg efgartigimod q7d. The findings resolved by the end of the recovery period. It was also found that administration of efgartigimod had no impact of the ability of PBMCs to respond to KLH antigen recall as confirmed by secretion of IFN-γ in ELISpot assays.

The following is already included in SmPC: *The potential interaction with vaccines was studied in a nonclinical model using Keyhole limpet hemocyanin (KLH) as the antigen. The weekly administration of 100 mg/kg to monkeys did not impact the immune response to KLH immunisation. Nevertheless, all vaccines should be administered according to immunisation guidelines and at least 4 weeks before initiation of a treatment cycle and not until 2 weeks after the last infusion of a treatment cycle. For patients that are on treatment, vaccination with live or live attenuated vaccines is not recommended (see section 4.4).*

2.4.5. Ecotoxicity/environmental risk assessment

Efgartigimod alfa is a recombinant protein and, due to the nature of the product, is unlikely to result in significant risk to the environment. As per the EMA Guideline EMEA/CHMP/SWP/4447/00 corr 2, Section 2, the MAH did not submit environmental risk assessment studies.

2.4.6. Discussion on non-clinical aspects

A brief number of studies were submitted in support of this line extension to include SC administration. A new PD study was submitted, which investigated the interaction between IV administered efgartigimod and IVIg treatment in Tg32 mice. Furthermore, a PD/PK study in male cynomolgus monkeys examined the pharmacokinetic properties after SC or IV administration of 30 or 100 mg/kg efgartigimod (without inclusion of rHuPH20).

Two new nonclinical toxicity studies were submitted, one 12-week repeat dose bridging study in cynomolgus monkeys, and a local tolerance study in rabbits. Neither study revealed any pertinent concerns regarding the SC formulation of efgartigimod. In addition, the TDAR evaluation was extensively presented and discussed by

the MAH, but the study had actually been submitted, and the relevant information already included in the SmPC (Section 4.4) since MAA approval for the IV route of administration.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, efgartigimod SC is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Overall, the provided brief newly submitted nonclinical study package, supported by the knowledge from the initial MAA including IV administration of efgartigimod can be considered sufficient to support the line extension for efgartigimod SC.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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.

A high-level overview and details on the PK, PD and immunogenicity sampling are provided below for healthy participants and participants with gMG, respectively.

- **Tabular overview of clinical studies**

Table 4: Summary of available data for efgartigimod

Study	ARGX-113-1501 (SAD)	ARGX-113-1501 (MAD)	ARGX-113-1602	ARGX-113-1702	ARGX-113-1704[a]	ARGX-113-1901	ARGX-113-1907	ARGX-113-2001	ARGX-113-2002
Phase Subjects Administration	Phase 1 Healthy subjects IV infusion 2h	Phase 1 Healthy subjects IV infusion 2h	Phase 2 Patients with gMG IV infusion 2h	Phase 1 Healthy subjects IV infusion 2h and 1h, SC	Phase 3 Patients with gMG IV infusion 1h	Phase 1 Healthy subjects PH20 SC	Phase 1 Healthy subjects IV infusion 1h, PH20 SC	Phase 3 Patients with gMG IV infusion 1h, PH20 SC	Phase 3 Patients with gMG PH20 SC
Treatment	0,2, 2, 10, 25, 50 mg/kg	10, 25 mg/kg	10 mg/kg	10 mg/kg and 300 mg	10 mg/kg	750, 1250, 1750 mg, 10 mg/kg	10 mg/kg (IV), 1000 mg (PH20 SC)	10 mg/kg (IV), 1000 mg (PH20 SC)	1000 mg
Treatment regimen	1 day	q4d on 6 occasions (10 mg/kg) QW on 4 occasions (10 and 25 mg/kg)	QW on 4 occasions	Single dose 2x20 mg/kg administered on Day 1 and 4 followed by 8 weekly 300 mg SC doses QW on 4 occasions	3-week treatment period (TP) of 4 weekly infusions (at visits 1-4). Re-treatment possible upon clinical deterioration. Minimum of 4 weeks between the last efgartigimod dose of a TP and a next TP	1 day	QW on 4 occasions	QW on 4 occasions	3-week treatment period (TP) of 4 weekly administrations (at visits 1-4). Re-treatment possible upon clinical deterioration. Minimum of 4 weeks between the last efgartigimod dose of a TP and a next TP
PK/PD sampling[b]	0, 2, 4, 8, 24, 48, 72, 96, 144, 336, 504, 672 h post infusion	q4d day 1, 5, 9, 13, 17: 0, 2, 8, 24, 48, 72 h post infusion q4d from day 21: 0, 2, 8, 24, 48, 72, 96, 144, 216, 336, 504, 672, 1008, 1344 h post infusion QW day 1, 8, 15: 0, 2, 8, 24, 72, 120 h post infusion QW from day 22: 0, 24, 48, 72, 120, 144, 216, 336, 504, 672, 1008, 1344 h post infusion	day 1, 5[c], 8, 12[c], 15, 19[c], 22, 26[c], 29, 36, 43, 50, (57, 64, 71 and 78)[d]	Single dose: 0, (1, 2, 4, 8, 12)[e], 24, (36)[e], 48, 72, 96, 120, 144, 192, 240, 336, 504, 672, 1008 h Repeated dose: day 1, 4, 8, 22, 29, 36, 43, 50, 57, 58, 59-63, 65, 67, 71, 78[e], 85[e], 99[e], 113[d,e]	day 1, 8, 15, 22, 29, 36, (43, 50, 57)[d] and 182. For Japanese patients, additional PK samples were taken after the first and the fourth infusions (i.e, days 2 and 4)	day 1, 2, 3, 4, 5, 6, 7, 9, 11, 15, 22, (29, 43 and 56)	PK: day 1[f], 8[f], 15[f], 22[g], 23, 24, 25, 26, 27, 29, 36, 50, 64, 78 PD: day 1, 8, 15, 22, 23, 24, 25, 26, 27, 29, 36, 50, 64, 78	PK: day 1[f], 8[f], 15[f], 22[g], 29, 36, 43, 50, 57 and 71 PD: day 1, 8, 15, 22, 29, 36, 43, 50, 57 and 71	PK (pre-dose only)[h]: day A, A+2[i], A+23[i], A+28, ET/SFU, EoS PD[h]: day A, A+7[j], A+14[j], A+21[j], A+28, Y+21, ET/SFU, EoS
Nr. of subjects	6 per cohort (4 active, 2 placebo)	8 per cohort (6 active, 2 placebo)	24 (12 active, 12 placebo)	8 or 16 active per cohort	84 active, 83 placebo	8-9 active per cohort	27 active per cohort	55 per cohort (SC and IV)	
Total nr. of subjects	30	32	24	40	167	33	54	110	164

a Active and placebo subjects in study ARGX-113-1704 could roll over into study ARGX-113-1705, which was a single-arm open-label extension study in which gMG patients underwent a variable number of treatment periods. Similar to the efgartigimod treatment regimen as applied in ARGX-113-1704, a 10 mg/kg dose of efgartigimod was administered weekly for three weeks (four infusions) as a 1-hour IV infusion at Visits 1, 2, 3, and 4 of each treatment period. With the exception

of patients who discontinued early from study ARGX-113-1704, all participants of ARGX-113-1704 who reached the end-of-study visit were allowed to roll-over into study ARGX-113-1705. Total IgG and binding AChRAb information was only available up to 1 year after the start of study ARGX-113-1705.14
b Based on study protocols
c only taken in a limited number of patients (i.e. five)
d pD only
e PK only
f pre-dose for IV and PH20 SC and 1 hour post dose for IV
g pre-dose and 4, 8, 12 hours post dose for IV and PH20 SC and 1 hour post dose for IV
h A: day 1 of a treatment period, Y: previous intertreatment period visit. ET /SFU : End of Treatment/Safety Follow-Up visit, EoS: End of Study visit ;
I optional PK visits in cycle 1 and/or cycle 2, approximately 48 hours (±1 day) after the 1st and 4th administration
j MG-ADL score only

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Efgartigimod alfa is a IgG1-derived Fc fragment produced by recombinant DNA technology. Efgartigimod alfa is engineered for increased affinity to the FcRn, resulting in the reduction of the levels of circulating IgG including autoantibodies. Efgartigimod alfa has been developed for treatment of adult patients with gMG. The molecular weight of efgartigimod alfa is approximately 54 kDa.

The MAH has been granted a marketing authorisation for efgartigimod as an IV product, and the present line extension concerns a fixed dose of 1000 mg efgartigimod coformulated with the permeation enhancer rHuPH20 (2000 U/mL) for SC administration. The proposed posology is 1000 mg efgartigimod once weekly for four weeks with subsequent treatment cycles according to clinical evaluation, the same administration regimen as with IV administration.

The clinical pharmacology of efgartigimod PH20 SC has been studied in both healthy participants (studies ARGX-113-1901 and ARGX-113-1907) and participants with gMG (studies ARGX-113-2001 and ARGX-113-2002).

Analytical methods

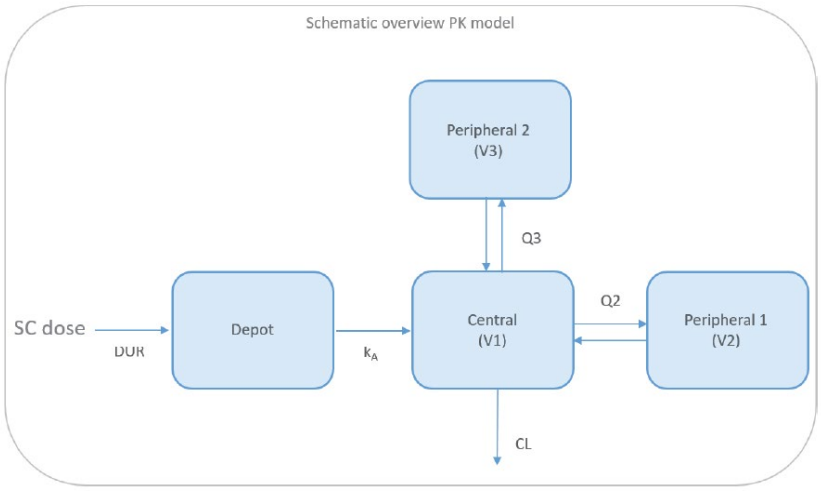
Ten clinical bioanalytical reports were submitted with this extension and covered quantification of efgartigimod in study 2001, 1907 and 1901, determination of PD markers in studies 2001, 1907, 1901, 1704 and 1705, detection of efgartigimod ADAs in study 2001, 1907 and 1901, rHuPH20 ADAs in study 2001, 1907 and rHuPH20 neutralizing antibodies (Nabs) in study 2001.

Several validated analytical methods were employed for quantification of efgartigimod, for detection of PD markers and for assessment of immunogenicity of efgartigimod and of rHuPH20.

Population PK (popPK) analyses including Study 2001

The popPK model for efgartigimod PH20 SC was based on a 3-compartment PK model submitted for the approved IV treatment. This model contained the assumption that volume of peripheral components (V2 = V3) and interindividual variability (IIV) was included on clearance (CL), volume of central compartment (V1), V2/V3, first order absorption rate (Ka) and CLxV1 covariance. The model structure is shown in figure below. The PopPK included data from healthy subjects (ARGX-113-1501, ARGX-113-1702 (IV data only), ARGX-113-1901, ARGX-113-1907) and gMG patients (ARGX-113-1602 and ARGX-113-1704) after either efgartigimod IV or efgartigimod PH20 SC treatment. Absorption following efgartigimod PH20 SC administration was modelled using a sequential zero-first order absorption model with a short or a long duration of the zero-order absorption.

Figure 2: Schematic representation of the PK model for efgartigimod

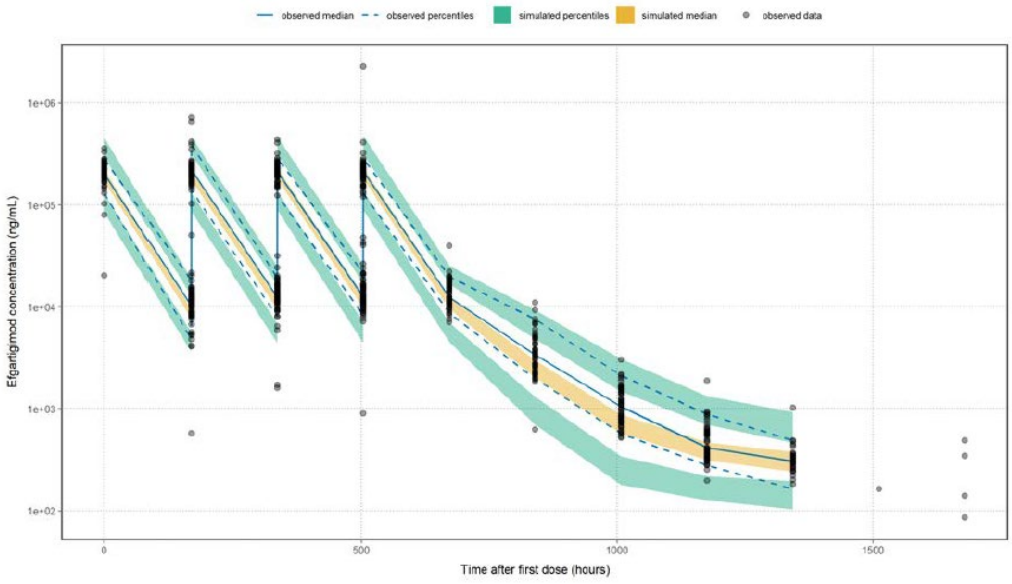


Schematic representation of the PK model for efgartigimod. A three-compartmental model was used to describe the PK of efgartigimod. It was assumed that the volumes of the two peripheral compartments were the same, i.e. V2=V3. CL=clearance of efgartigimod; V1: volume of central compartment: Q2 and Q3: inter-compartmental flow; V2=V3 volume of peripheral compartments; DUR: duration of the zero-order absorption; KA: first-order abs rate.

The previous model was updated with data from study ARGX-113-2001 with re-estimation of parameters. Significant covariates were: body weight on CL, V1 and V2/V3, estimated glomerular filtration rate (eGFR) on CL and sex on V1. The final parameters were estimated with adequate precision (%RSE). Eta shrinkage was <20% except for Ka (36%) and V2/V3 (36.9%).

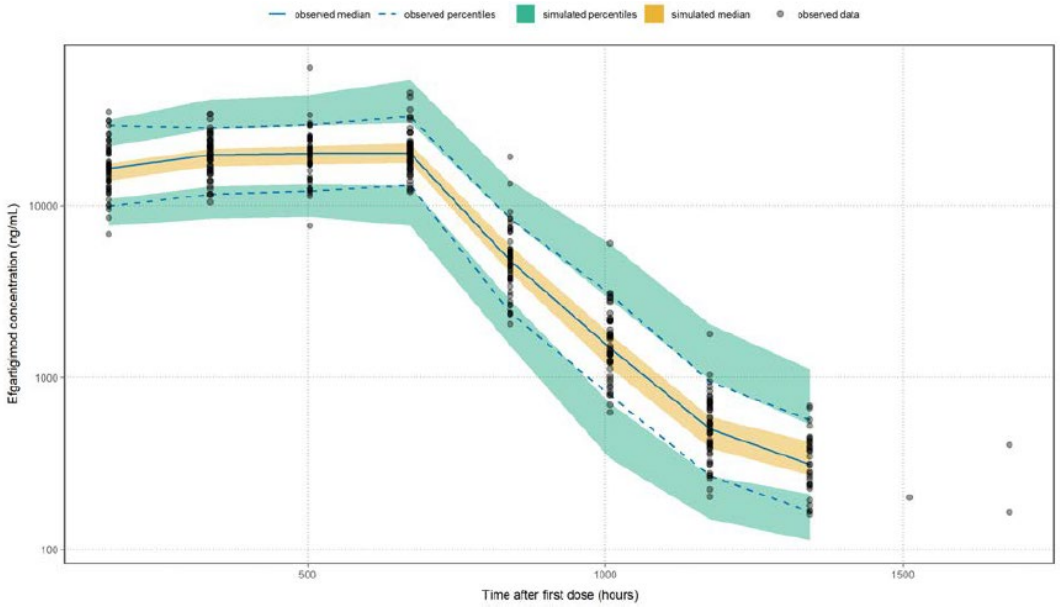
The final model was evaluated by goodness of fit (GoF) plots and prediction corrected visual predictive checks (pcVPCs). pcVPCs for Study 2001 (IV and SC) are displayed in figures below.

Figure 3: Prediction-corrected visual predictive checks: efgartigimod PK in ARGX-113-2001 (IV treatment arm), obtained with the final PK model



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

Figure 4: Prediction-corrected visual predictive checks: efgartigimod PK in ARGX-113-2001 (PH20 SC treatment arm), obtained with the final PK model



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

None of the significant covariates sex, eGFR and body weight were considered to have clinically relevant impact on efgartigimod SC exposure. Table below shows the impact of weight after 10 mg/kg IV or 1000 mg SC treatment.

Table 5: Impact of a single isolated covariate on AUC0-168h compared to a reference subject after the fourth weekly doses of efgartigimod

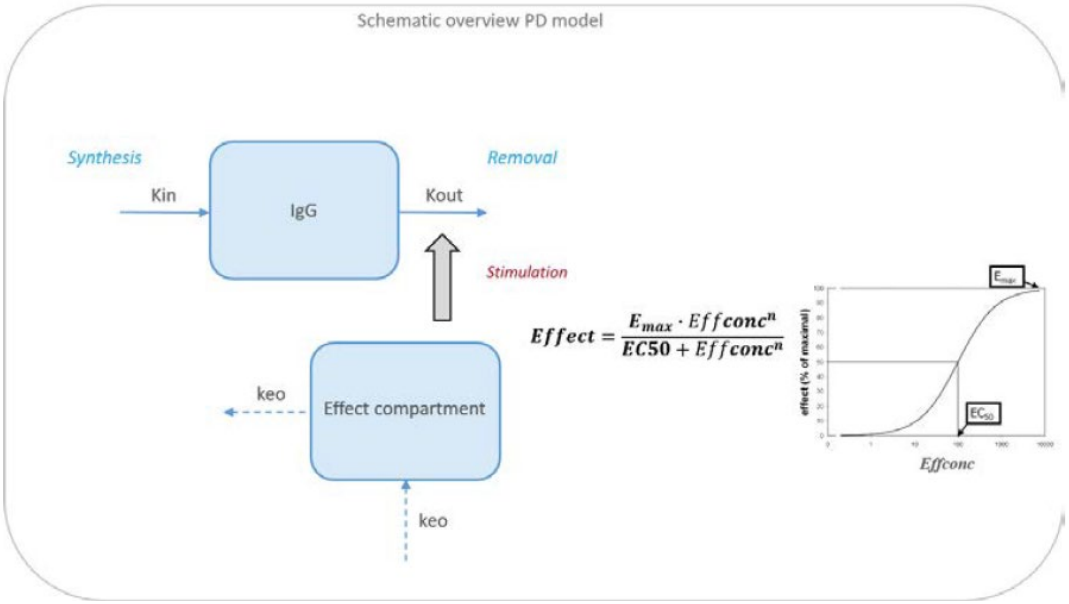
Covariates	10 mg/kg IV		1000 mg PH20 SC	
	Value[a]	Relative change AUC_{0-168h}[b]	Value[a]	Relative change AUC_{0-168h}[c]
Weight 5th perc.	52.9	-18.4% (90%CI: -22.8%, -13.7%)	50.4	+22.5% (90%CI: +15.8%, +29.5%)
Weight 95th perc	120[d]	+26.7% (90%CI: +21.6%, +32.0%)	112	-15.4% (90%CI: -20.4%, -10.1%)
eGFR 5th perc.	60.2	+27.5% (90%CI: +22.8%, +32.5%)	72.0	+16.8% (90%CI: +10.9%, +22.9%)
eGFR 95th perc.	123	-9.04% (90%CI: -12.2%, -5.66%)	129	-11.3% (90%CI: -15.2%, -7.16%)

A Weight in kg and eGFR in ml/ min/ l.73m2
B compared to a reference subject with median body weight and eGFR (77.3 kg and 100.71 ml/ min/l.73m2) in ARGX-113-1704/ ARGX-113-2001 IV treatment. The forest plots were constructed by assuming male gMG patients as reference population, but comparable results were obtained when assuming a female population (results not shown)
C compared to a reference subject with median body weight and eGFR (78.3 kg and 100.32 ml/ min/ 1.73m2) in ARGX-113-2001 PH20 SC treatment. The forest plots were constructed by assuming male gMG patients as reference population, since it represented the majority in the combined dataset, but comparable results were obtained when assuming a female population (results not shown)
D for the 10 mg/ kg efgartigimod IV arm, 120 kg is reported, instead of the 95th percentile of body weight

PK/total IgG model including Study 2001

The existing PK/total IgG model including data from studies 1501, 1602, 1702, 1704, 1901 and 1907 was updated with data from Study 2001. The model structure was an indirect response model with an effect compartment to describe the time delay between efgartigimod concentrations and the reduction of total lgG concentrations. See Figure below IIV was included for baseline, concentration in the effect compartment providing half of the maximum effect (EC_{50}), degradation rate (kout) and first-order delay rate constant (keo), and a proportional error model for the residuals. Covariance was found between EC_{50} and kout, and between $EC_{50}$and keo. The significant covariates identified in the updated model were IVMG on EC_{50}, co-medication on baseline and population type on kout.

Figure 5: Schematic representation of the PK/PD model of total IgG

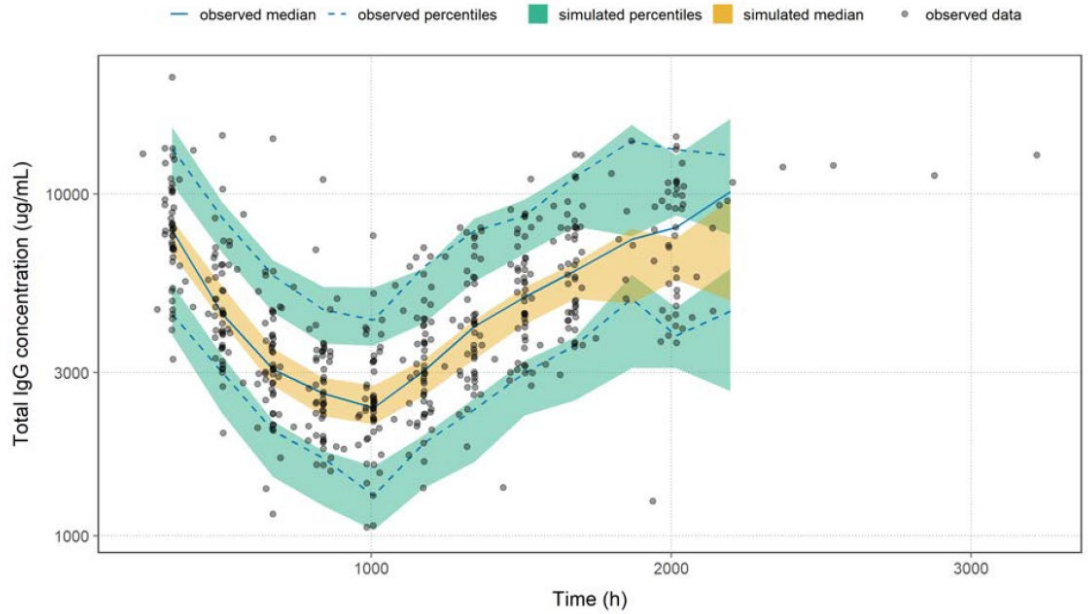


Schematic representation of the PK/PD model for total IgG. An indirect response model described the total IgG concentration and the concentration of efgartigimod in the effect compartment stimulated the removal of total IgG from the system. The applied concentration-effect relationship for stimulation of the removal rate by efgartigimod was a sigmoidal E_{max} model. Kin: production rate; kout: degradation rate: E_{max}: maximum effect; EC_{50} efgartigimod concentration in the effect compartment providing half of the maximum effect: Effconc: efgartigimod concentration in the effect compartment: keo: first-order delay rate constant: n: shape parameter.

Eta-shrinkages were 2.02%, 24.78%, 26.90% and 45.20% for BL, EC_{50}, kout and keo, respectively.

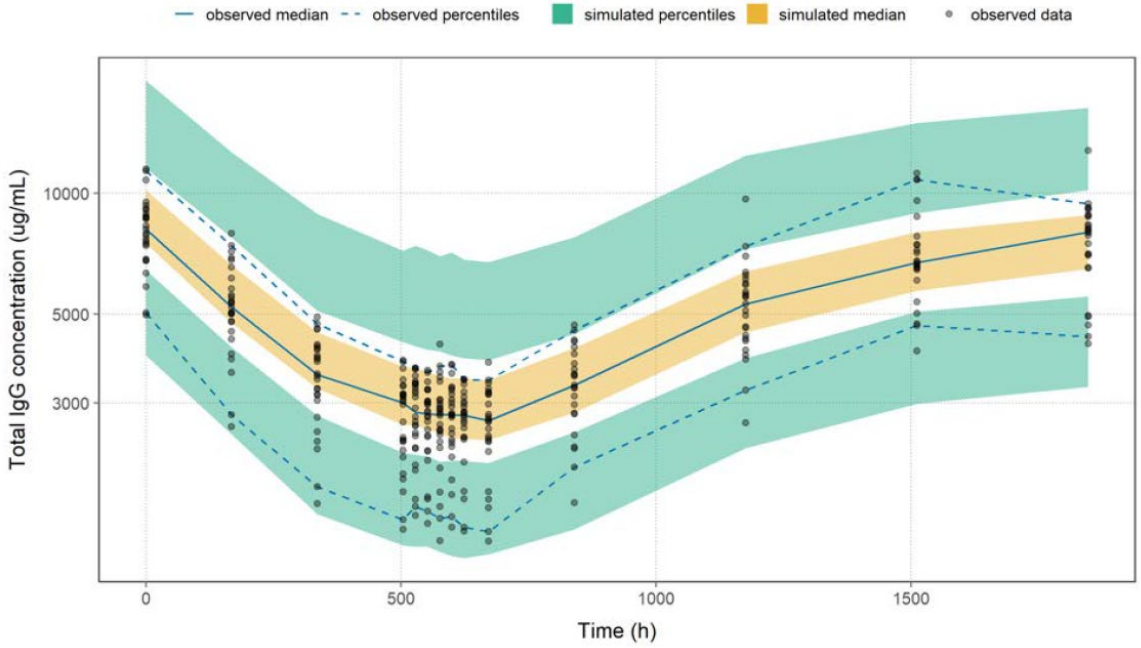
The pcVPCs of IgG data collected after SC dosing across the various studies in the data population including an external fit of the data from Study 2002 are displayed in Figures below.

Figure 6: Prediction-Corrected Visual Predictive Checks: total IgG concentration in ARGX-113-2001 (PH20 SC treatment arm), obtained with the final PK/total IgG model (M.tIgG.mod)



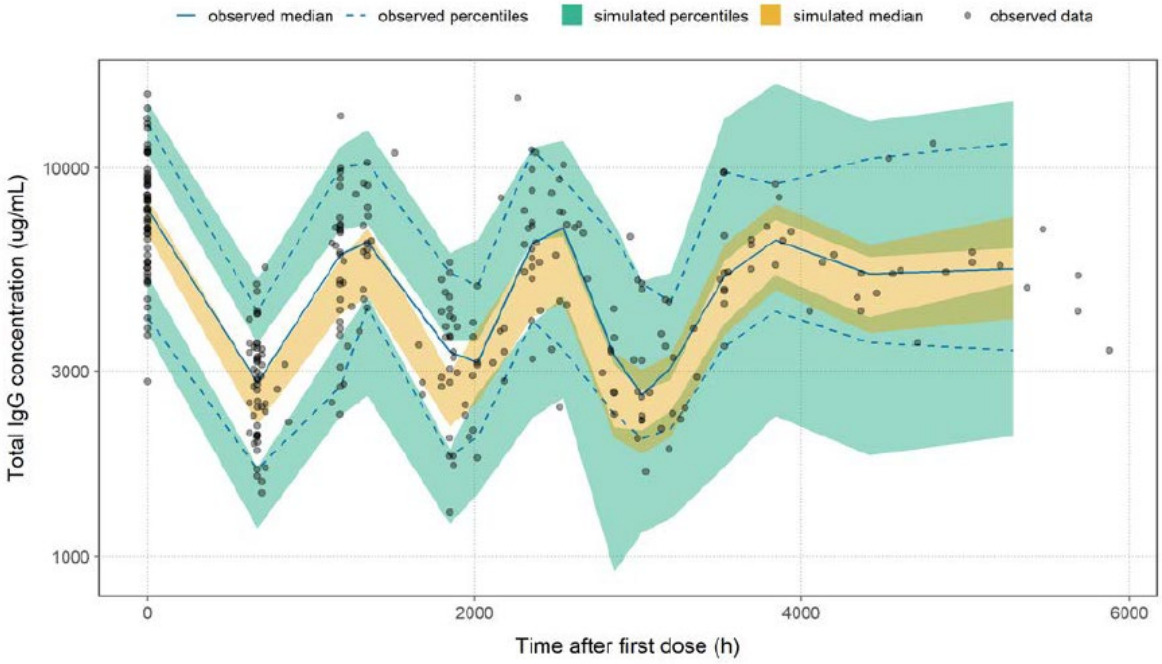
Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 7: Prediction-Corrected Visual Predictive Checks: total IgG concentration in ARGX-113-1907 (PH20 SC treatment arm), obtained with the final PK/total IgG model (M.tIgG.mod)



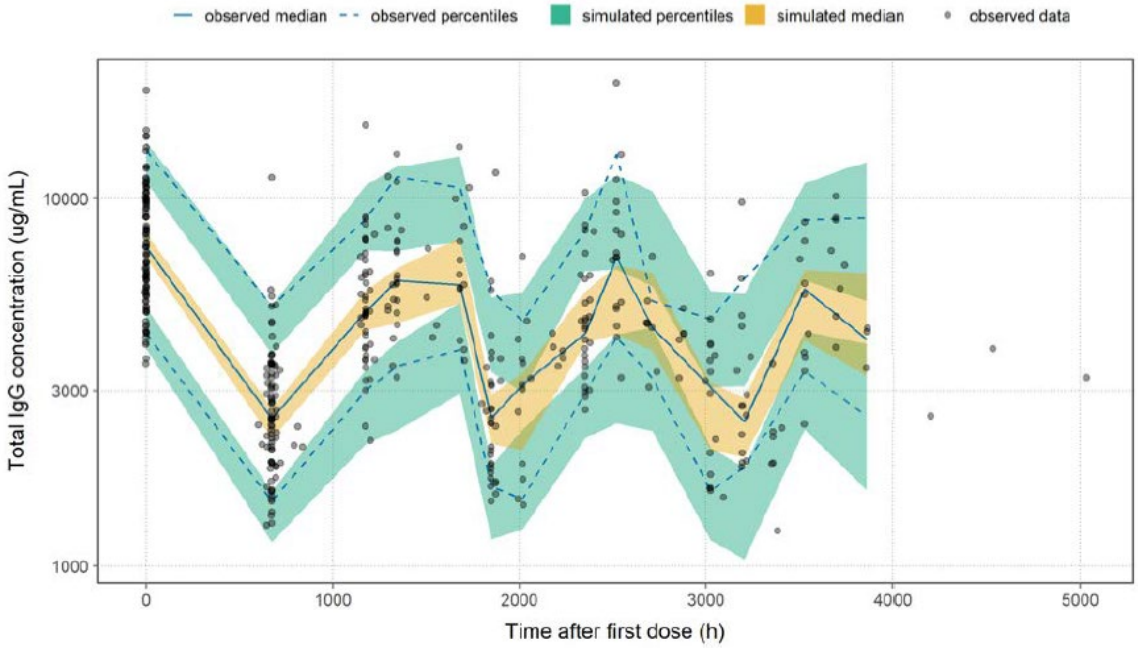
Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 8: Prediction-Corrected Visual Predictive Checks: prediction of total IgG concentration obtained with the model N.tIgG.mod (ARGX-113-2002, PH20 SC treatment arm, patients rolling over from ARGX-113-1705)



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

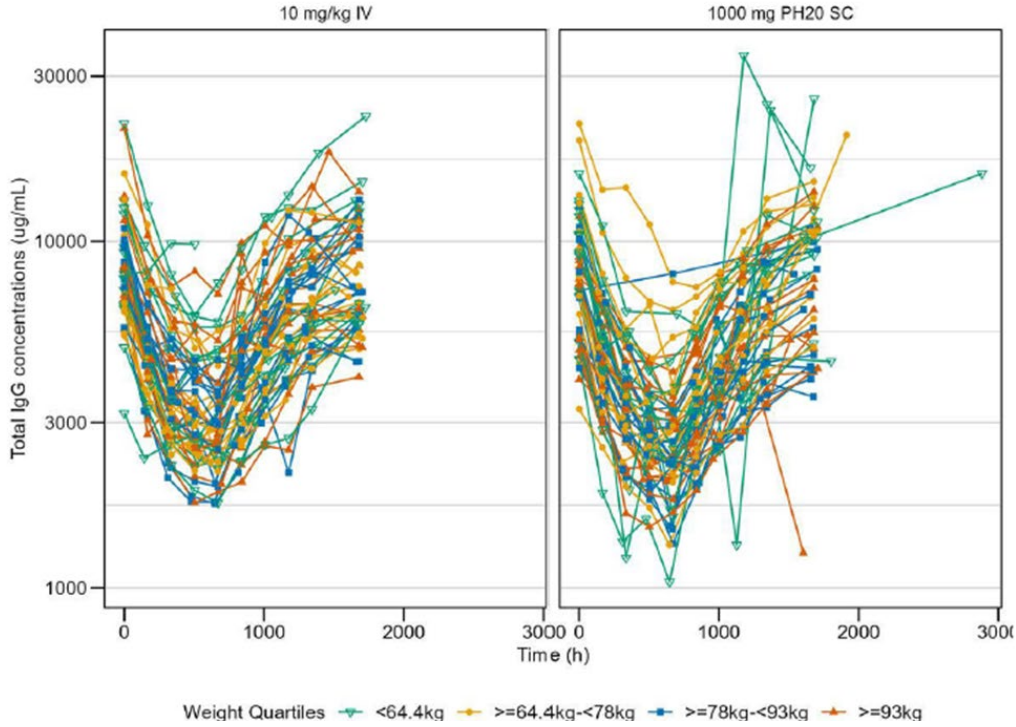
Figure 9: Prediction-Corrected Visual Predictive Checks: prediction of total IgG concentration obtained with the model N.tIgG.mod (ARGX-113-2002, PH20 SC treatment arm, patients rolling over from ARGX-113-2001)



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

Individual total IgG observations from Study 2001 colour coded by body weight quartiles are shown in Figure below stratified for treatment.

Figure 10: Individual total IgG concentration-time profiles in Study ARGX-113-2001



IgG=immunoglobulin gamma, IV=intravenous; SC=subcutaneous
Note Dots represent observations, with connecting lines indication all observations belonging to a specific individual. Color coding was added per weight quartile based on the overall weight at baseline.

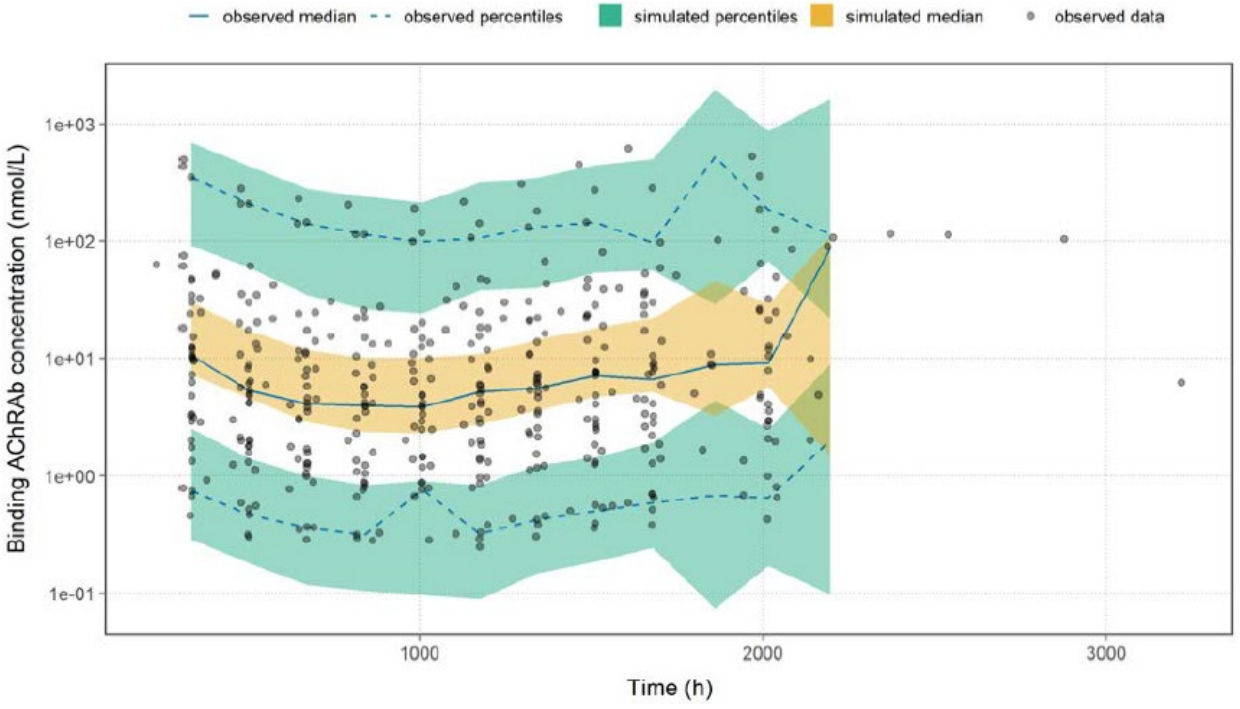
PK/total lgG/binding AChRAb model including Study 2001

The existing PK/total IgG/binding AChRAb model based on the final PK/total IgG model and AChRAb data collected in seropositive and in seronegative gMG patients from IV studies 1602 (n=12) and 1704 (n=84), was updated with AChRAb data collected in seropositive patients from Study 2001. The model parameters were re-estimated, however, parameters and effects that came from the final PK/total IgG model were fixed. The model assumes that AChRAb is a subset of total lgG. IIV was only estimated for baseline binding AChRAb and the scaling parameter α.

The scaling parameter which describes the reduction in AChRAb as a function of the reduction in total lgG, was close to 1 in the final model (α=0.994). Covariate effects included was population (IV gMG) on EC_{50}, population (gMG) on kout and co-medication on baseline. Covariate effects were all fixed and came from the final PK/total IgG model and were thus related to the total IgG data.

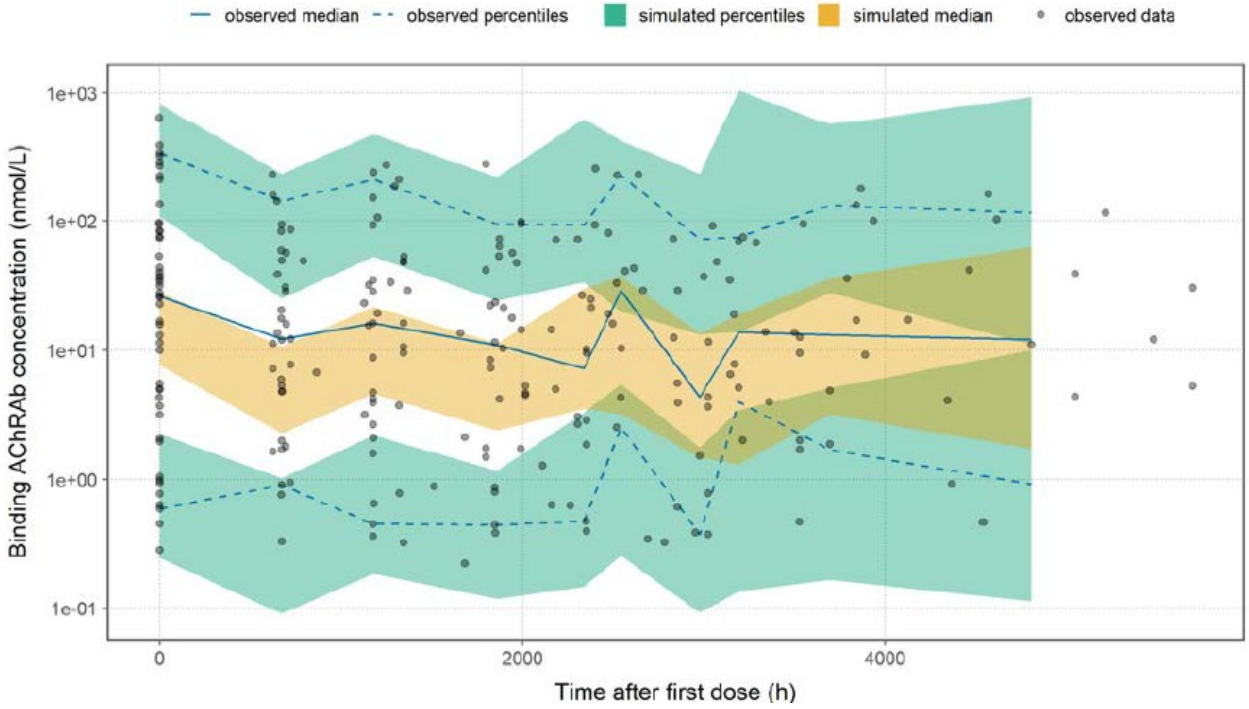
The final PK/total IgG/binding AChRAb model (C.AChRAb.mod) was evaluated by GoF plots and VPC's which indicated the model could describe the AChRAb observations in seropositive subjects from Study 2001. The PK/total lgG/binding AChRAb model was also applied to the binding AChRAb observations in seropositive patients from Study 2002. Here underprediction was visible for AChRAb concentrations approximately at TAD<1500 h, most pronounced in subjects rolling over from Study 1705. VPCs for Study 2001 (SC) and Study 2002 are shown in Figures below).

Figure 11: Prediction-Corrected Visual Predictive Checks: binding AChRAb concentration in ARGX-113-2001 (PH20 SC treatment arm), obtained with the final PK/total IgG/binding AChRAb model (C.AChRAb.mod)



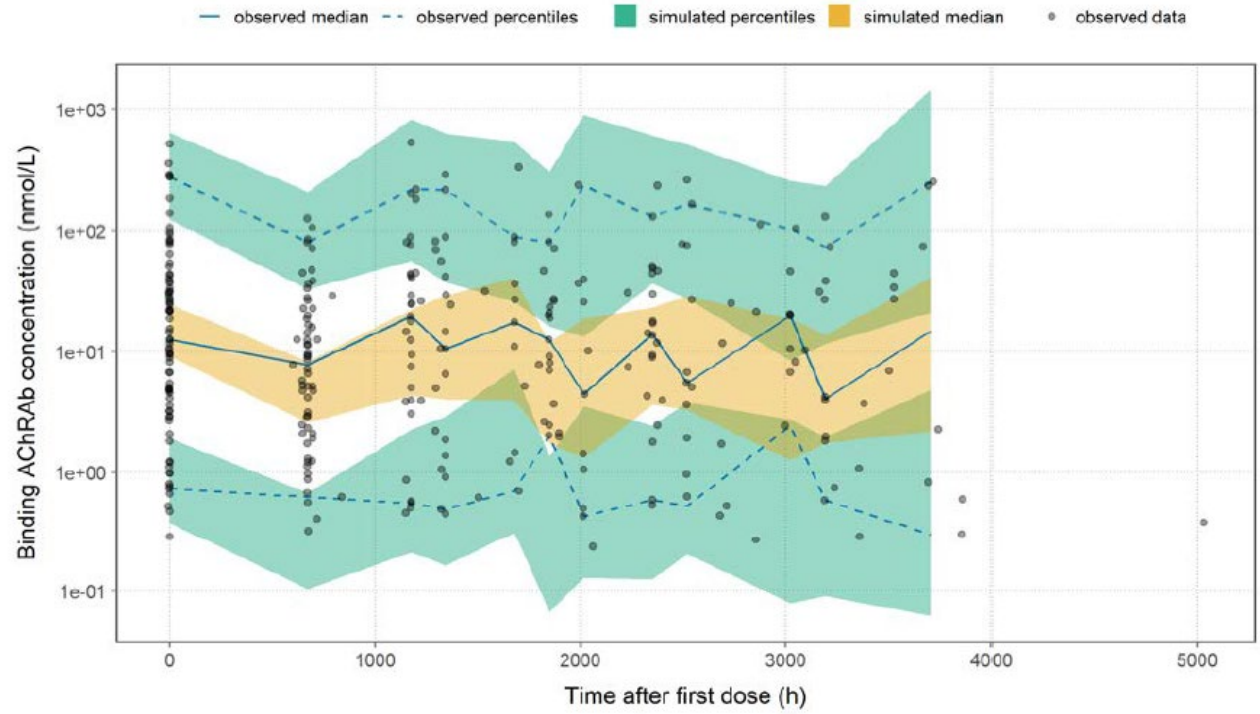
Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 12: Prediction-Corrected Visual Predictive Checks: prediction of AChRAb concentration obtained with the model D.AChRAb.mod (ARGX-113-2002, PH20 SC treatment arm, patients rolling over from ARGX-113-1705)



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

Figure 13: Prediction-Corrected Visual Predictive Checks: prediction of AChRAb concentration obtained with the model D.AChRAb.mod (ARGX-113-2002, PH20 SC treatment arm, patients rolling over from ARGX-113-1705)



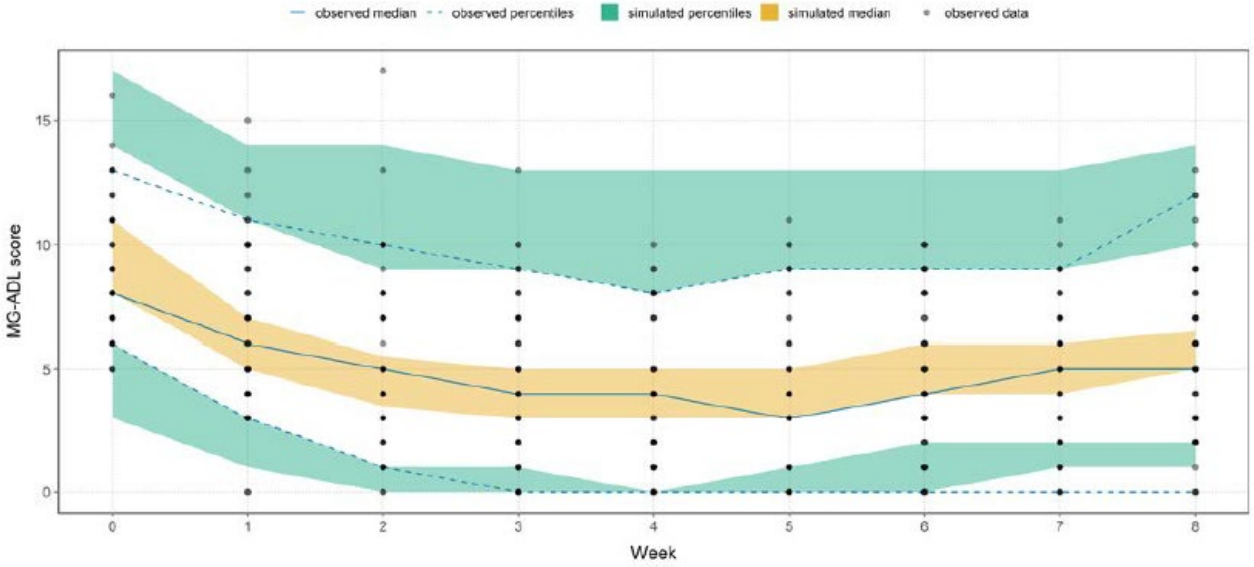
Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

MG-ADL score model including Study 2001

A bounded integer model for MG-ADL score with data from studies 1602, 1704 and 1705 (all IV dosed) was updated with MG-ADL score from study ARGX-113-2001 (IV and SC dosed) (B.MGADL.mod). The MG-ADL score data was collected in the first 8 weeks of a treatment cycle in both seropositive and in seronegative patients. The model included IIV on baseline and drug effect parameter α. The final PK/total lgG/binding AChRAb model was used to predict the binding AChRAb concentrations as a measure of drug effect at the time-points for MG-ADL scoring.

The responder rates for AChRAb seropositive patients in ARGX-113-2001 predicted by pre-final MG-ADL score model were in line with the observed. The VPC for SC patients of Study 2001 is shown below.

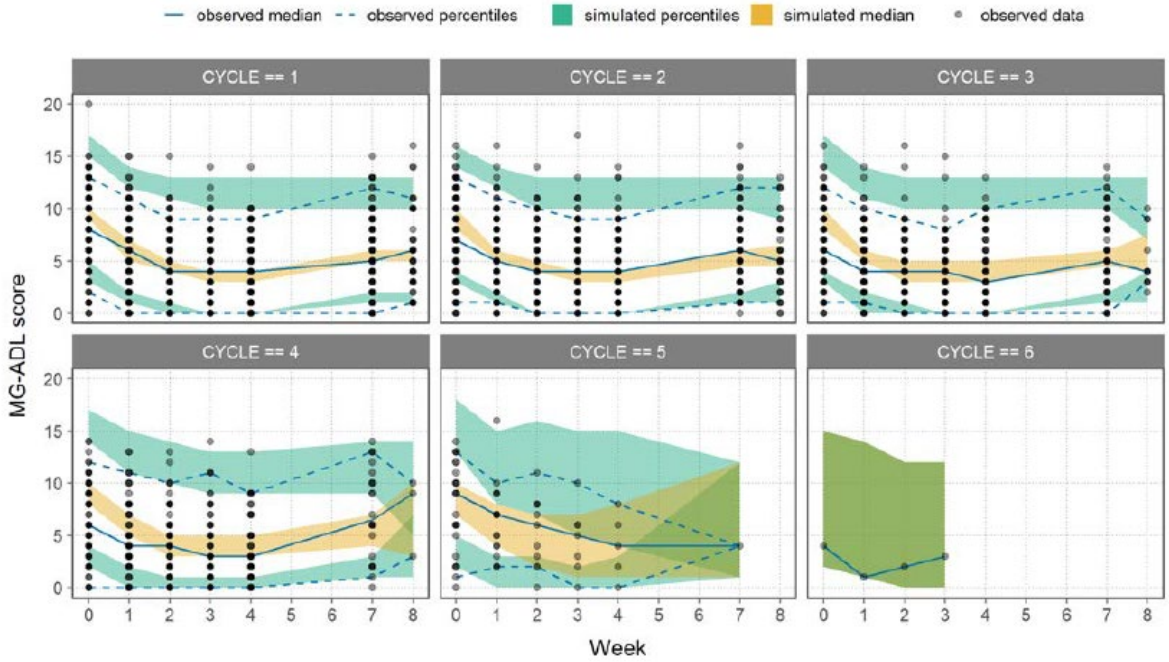
Figure 14: Visual Predictive Checks: MG-ADL score in patients receiving 1000 mg efgartigimod PH20 SC in ARGX-113-2001, obtained with the bounded integer model identified on MG-ADL score data from ARGX-113-1602, ARGX-113-1704, ARGX-113-1705, and ARGX-113-2001 (B.MGADL.mod)



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

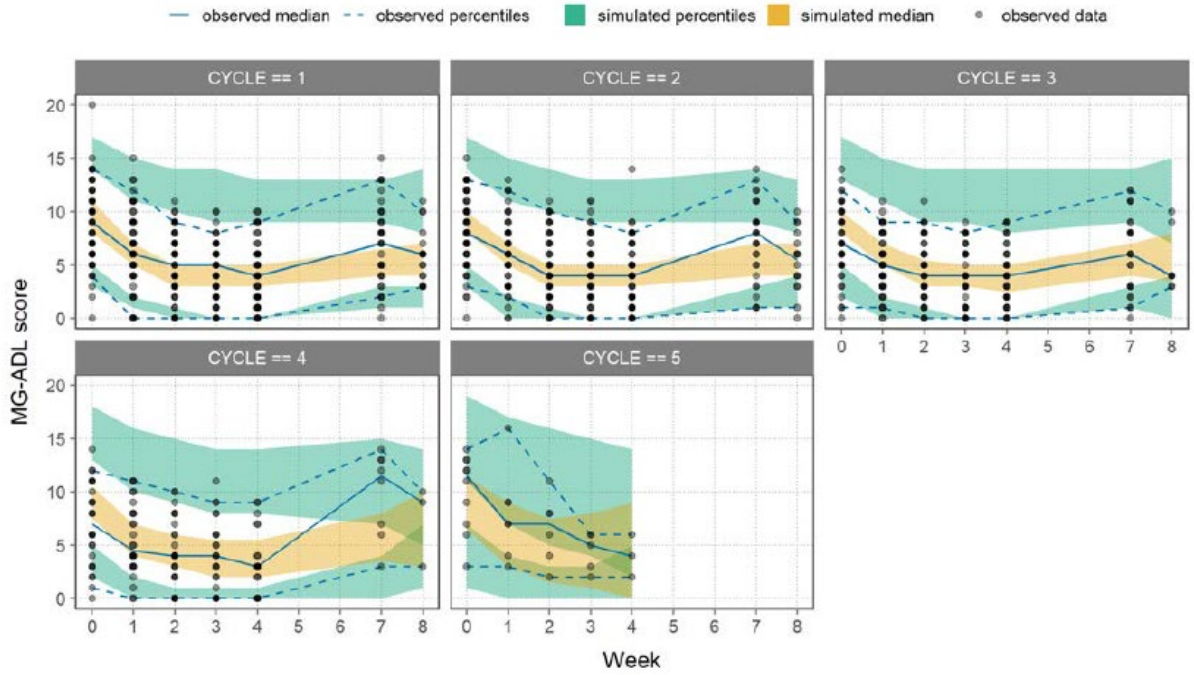
The final model reasonably well predicted the MG-ADL score observations from study ARGX-113-2002 (see Figures below), except for the baseline levels per cycle, suggested to be due to the different re-treatment criteria in that study as compared to ARGX-113-1704 and ARGX-113-1705.

Figure 15: Visual Predictive Checks: MG-ADL score in patients receiving 1000 mg efgartigimod PH20 SC in ARGX-113-2002, obtained with the bounded integer model identified on MG-ADL score data from ARGX-113-1602, ARGX-113-1704, ARGX-113-1705, and ARGX-113-2001 and used to predict data from ARGX-113-2002 (C.MGADL.mod)



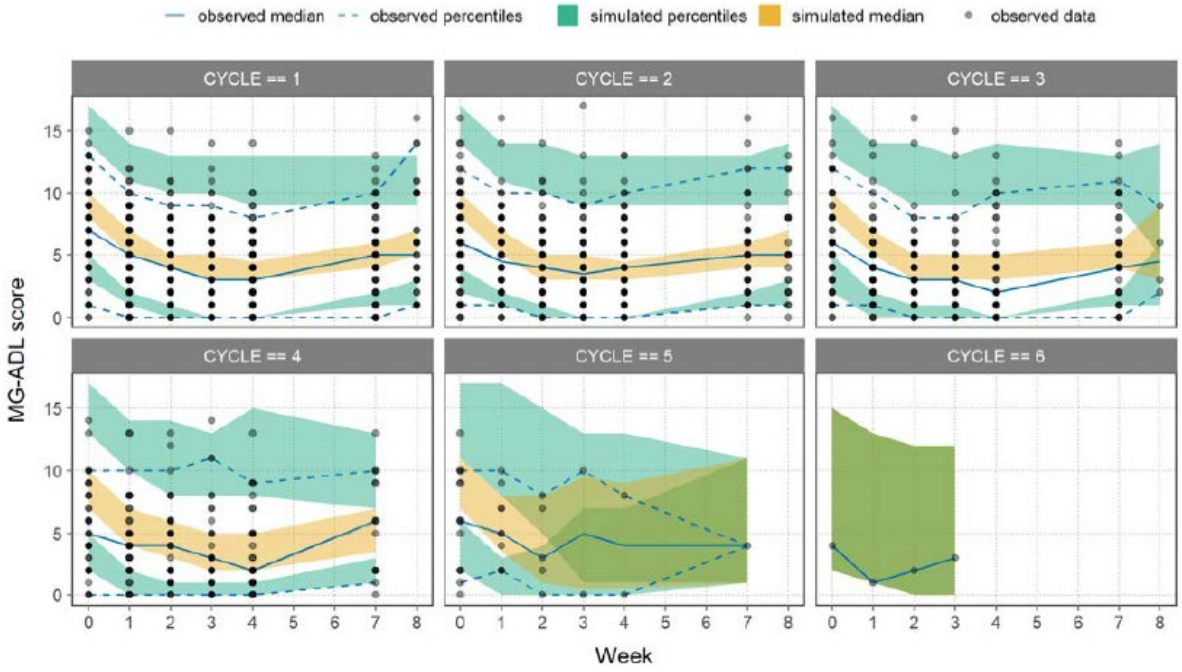
Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

Figure 16: Visual Predictive Checks: MG-ADL score in patients receiving 1000 mg efgartigimod PH20 SC in ARGX-113-2002, obtained with the bounded integer model identified on MG-ADL score data from ARGX-113-1602, ARGX-113-1704, ARGX-113-1705, and ARGX-113-2001 and used to predict data from ARGX-113-2002 (C.MGADL.mod)



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

Figure 17: Visual Predictive Checks: MG-ADL score in patients receiving 1000 mg efgartigimod PH20 SC in ARGX-113-2002 (patients rolling over from ARGX-113-1705), obtained with the bounded integer model identified on MG-ADL score data from ARGX-113-1602, ARGX-113-1704, ARGX-113-1705, and ARGX-113-2001 and used to predict data from ARGX-113-2002 (C.MGADL.mod)

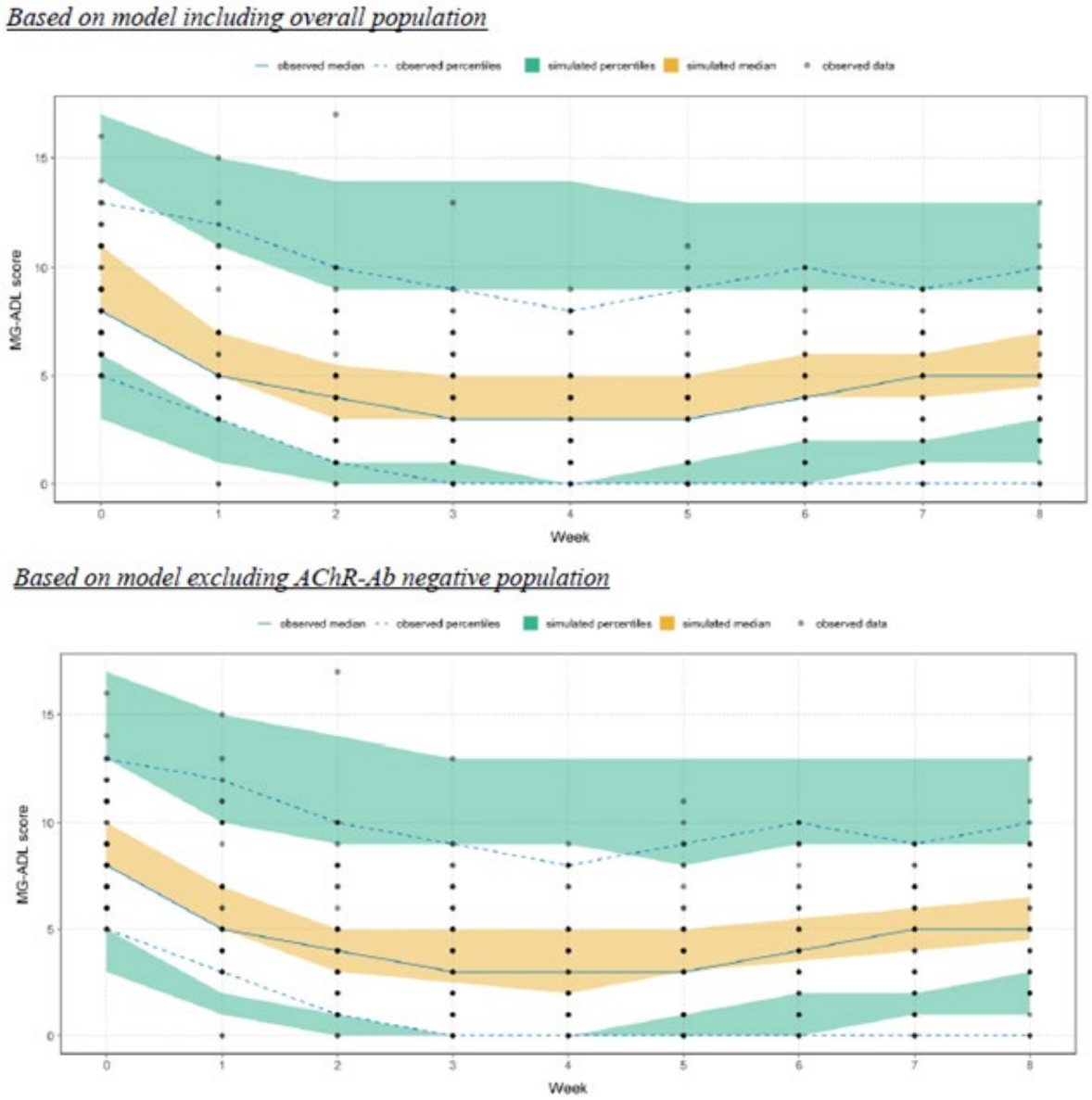


Grey dots: observations; blue solid line: observed median; blue dashed lines: 5th and 95th percentiles of observations; yellow area: 95% confidence interval for the predicted median; green areas: 95% confidence interval for the 5th and 95th percentiles of the prediction interval.

In the MG-ADL total score model, the reduction in total IgG was directly linked to the reduction of AChR-Ab, which is linked to the MG-ADL response. This model also included data from 57 AChR-Ab seronegative gMG patients. The population MG-ADL total score model was updated by excluding all AChR-Ab seronegative participants.

VPCs of MG-ADL total score in seropositive patients from Study 2001 following 100 mg SC dosing based on the first model and on the updated model are shown in Figure below for comparison.

Figure 18: visual predictive checks of MG-ADL total score in AChR-Ab seropositive participants receiving efgartigimod PH20 SC 1000mg in Study ARGX-113-2001



AChR-Ab=acetylcholine receptor antibody; MG-ADL=Myasthenia Gravis activities of Daily living; PI=Prediction interval; SC=Subcutaneous.

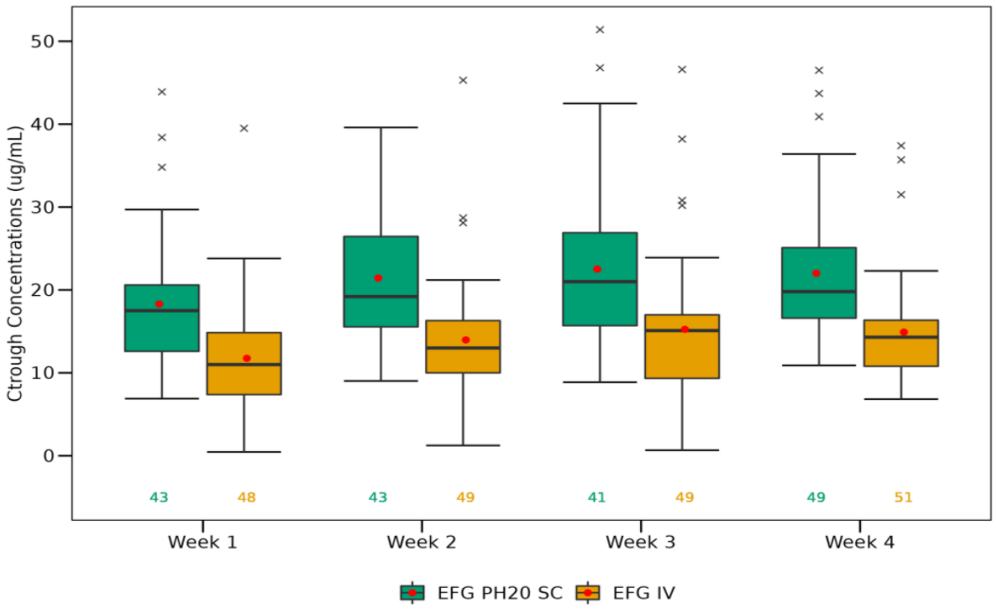
Absorption

As efgartigimod is a therapeutic protein, no dedicated absorption, distribution, metabolism and excretion study was performed. Based on popPK modelling, the estimated bioavailability after SC administration is 76.5%.

Concentration at the end of a dosing interval (Ctrough) data observed in the target population dosed with the intended 1000 mg SC (study 2001) are presented in Figure 19, and a comparison of exposure (C_{trough}) in healthy subjects and patients with gMG is presented in Figure 20**.** In patients with gMG, after each administration of efgartigimod PH20 SC 1000 mg, median Ctrough was 50% to 60% higher as compared to efgartigimod IV 10 mg/kg.

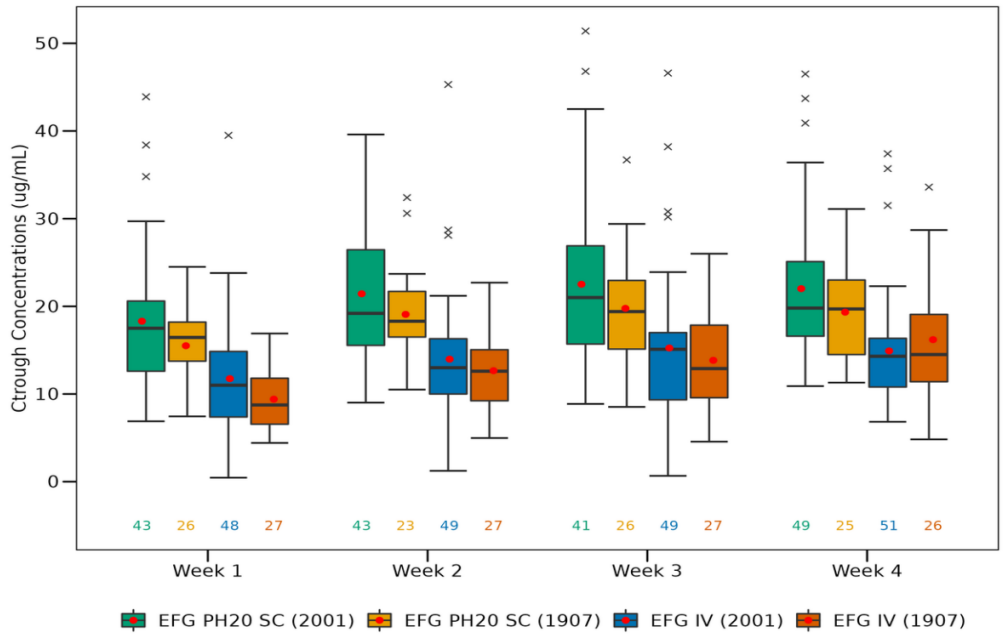
Based on popPK modelling, the median C_{max} and t_{max} after the fourth administration of efgartigimod SC are 48 µg/mL and 48 hours, respectively.

Figure 19: Efgartigimod Ctrough after 4 weekly administrations of efgartigimod PH20 SC 1000mg and Efgartigimod IV 10mg/kg in participants with gMG



Ctrough=serum concentration observed before the start of the administration at week 1, week 2, and week 3 and 1 week after the last administration on week 3 (ie, week 4); EFG=efgartigimod; IQR=interquartile range; IV=intravenous; SC=subcutaneous
Note: The solid line is the median; the red symbol is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile. The "X" indicates the outliers. One participant in the efgartigimod IV arm had a Ctrough value of 236 µg/mL at week 1, which is for graphical reasons not presented in the figure.

Figure 20: Boxplot of Ctrough after 4 weekly administrations of efgartigimod PH20 SC 1000mg and Efgartigimod IV 10mg/kg in healthy participants and participants with gMG



1907=study ARGX-113-1907: healthy participants; 2001=ARGX-113-2001: participants with gMG; Ctrough=serum concentration observed before the start of the administration at week 1, week 2, and week 3 and 1 week after the last administration on week 3 (ie, week 4); EFG=efgartigimod; IQR=interquartile range; IV=intravenous; SC=subcutaneous
Note: The solid line is the median; the red symbol is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value still within 1.5 IQR of the upper quartile. The "X" indicates the outliers. One participant in the efgartigimod IV arm of study ARGX-113-2001 had a Ctrough value of 236 µg/mL at week 1, which is for graphical reasons not presented in the figure. Values present the number of observations. Doses were administered at week 0, week 1, week 2, and week 3

The AChR-Ab serotype (seropositive or seronegative) had no effect on the C_{trough} of efgartigimod PH20 SC.

Distribution

Based on popPK data, the volume of distribution following subcutaneous efgartigimod is approximately 18 L.

Elimination

The route of elimination has been described in the original IV application. Once systemically absorbed, the elimination is the same regardless of the route of administration. In healthy participants, median values were comparable between both treatments and were 78.7 and 82.7 hours for efgartigimod IV and efgartigimod PH20 SC, respectively.

Dose proportionality and time dependencies

Dose proportionality has not been assessed after multiple SC dosing. After single SC doses of 750 to 1750 mg efgartigimod, a trend of more than dose-proportional increase in exposure with increasing SC doses cannot be excluded. However, the analyses are based on little data (n=8 in each dose group), so no conclusion can be made.

Based on the evaluation of C_{trough}, the accumulation of efgartigimod after the fourth administration compared to after the first administration of efgartigimod PH20 SC 1000 mg was minimal (Figure 19). Also, in subsequent cycles, the PK of efgartigimod did not change over time supported by consistent values of C_{trough} across the different cycles.

Inter-individual variability

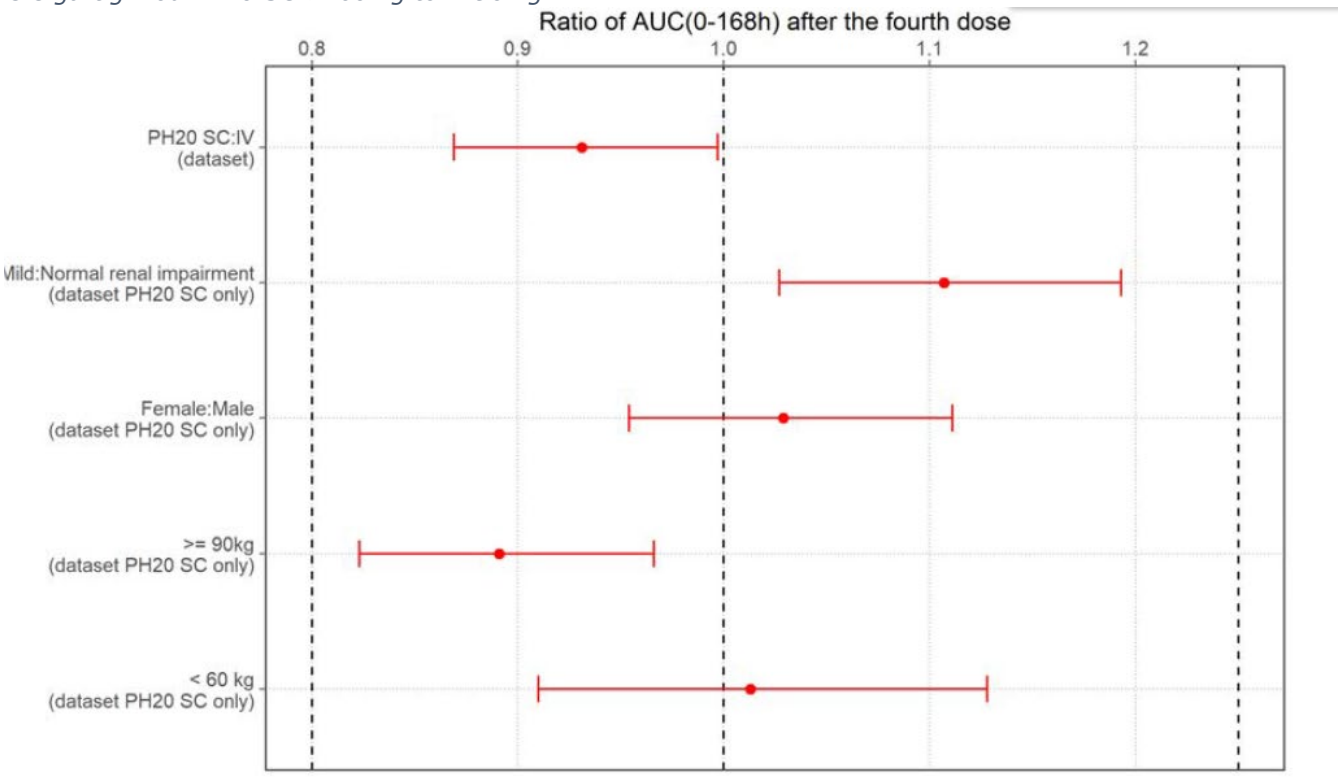
After 4 weekly administrations of efgartigimod PH20 SC 1000 mg in healthy participants, the intersubject variability in efgartigimod PK in %CV for C_{max} and $AUC_{0\text{-}168h}$ was 42.3% and 25.8%, respectively. In the population PK analysis on data from sparse sampling in phase 3 studies, the variability on the final PK model parameters CL, V1, and V2/V3 were moderate (ie, 19.5%, 34.0%, and 18.7%, respectively).

Special populations

Impaired renal function

In a categorical evaluation, patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2) were estimated to show a 11% (90% CI: 3% to 19%) higher $AUC_{0\text{-}168h}$, compared to patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2) (Figure 21). After 10 000 simulated replicates of the dataset, taking into account the underlying IIV and parameter uncertainty, the median, the 5th and 95th percentile of the 10 000 ratios with their 90% confidence interval (CI) were estimated to be 1.14 (90% CI: 1.03 to 1.25), 1.02 (90% CI: 0.92 to 1.12) and 1.28 (90% CI: 1.15 to 1.41) higher, respectively.

Figure 21: Forest plot to investigate potential differences in AUC_{0-168h} after four doses of efgartigimod resulting from PH20 SC versus IV administration and from body weight < 60 kg, body weight ⩾ 90 kg, female, and mild renal impairment patients (PH20 SC treatment arm only) (K.PK.mod). For body weight, the reference category is efgartigimod PH20 SC ⩾ 60 kg to < 90 kg.



AUC_{0-168} = area under the concentration time curve from time zero up to 168 hours; CI=confidence interval: IV=intravenous; SC=subcutaneous.
Red bar: ratio of AUC_{0-168h} after the fourth weekly dose based on the observed data. Red dot: median of AUC_{0-168h} ratio based on the dataset. Interval between the vertical connected solid red lines: 90% confidence interval of the AUC_{0-168h} ratio.
Vertical dashed lines: reference lines (0.8, 1, 1.25).

For body weight, the reference category is efgartigimod PH20 SC ≥60kg to <90 kg.

Impaired hepatic function

No participants with gMG and hepatic impairment have been studied. Therefore, no clinical data in participants with hepatic impairment are available, and the impact of hepatic impairment on the PK and PD of efgartigimod has not been studied. However, markers of hepatic function were evaluated as potential covariates in the pop PK/PD analysis. Albumin, total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) did not influence any of the model parameters in the final population PK/PD model.

Gender

After simulations of 4 weekly administrations of efgartigimod PH20 SC 1000 mg, based on the dataset of ARGX-113-2001, the median and 90% CI of the AUC_{0-168h} ratio for female compared to male patients was 1.02 (0.95 to 1.11). After 10 000 simulated replicates of the dataset, taking into account the underlying IIV and parameter uncertainty, the median, the 5th and 95th percentile of the 10 000 ratios with their 90% CI were estimated to be 1.10 (1.0 to 1.20), 0.98 (0.89 to 1.08) and 1.23 (1.11 to 1.35) higher, respectively.

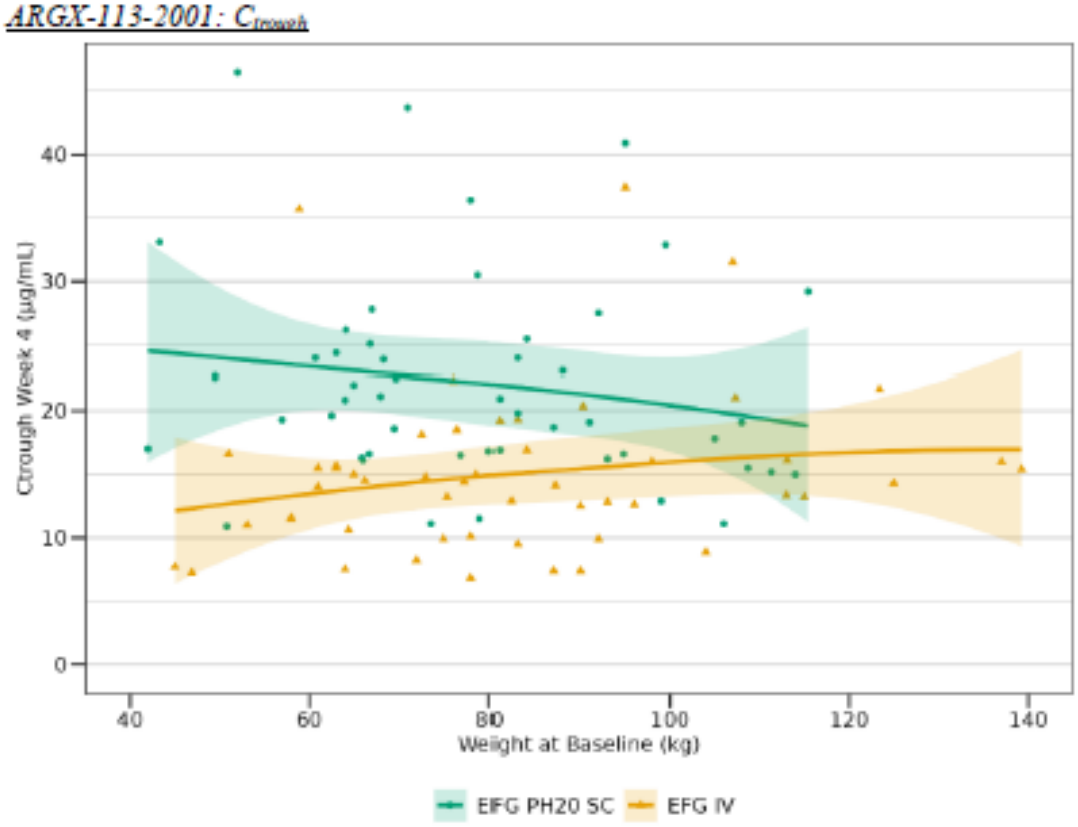
Weight

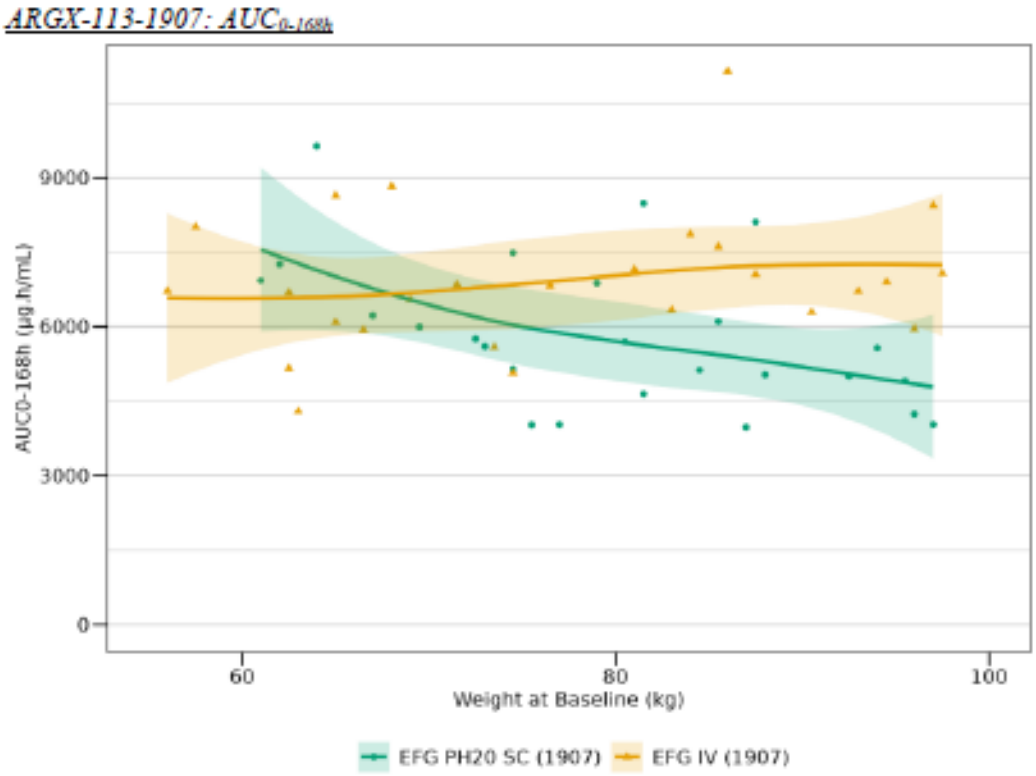
Evaluations to assess the effect of body weight on the exposure of efgartigimod PH20 SC are discussed below. The results of all analyses indicate that the effect of body weight on the exposure of efgartigimod is limited and not clinically relevant.

Based on the final popPK model, the $AUC_{0\text{-}168h}$ after the fourth administration of efgartigimod PH20 SC 1000 mg was simulated for a participant with the 5th and 95th percentile body weight (50.4 and 112.1 kg, respectively). The influence of body weight on efgartigimod exposure after administration of efgartigimod PH20 SC 1000 mg was limited with the simulated fold change in $AUC_{0\text{-}168h}$ relative to the median body weight of 78.3 kg within the bioequivalence boundaries of 0.8 to 1.25 (1.23- and 0.85-fold change for the 5th and 95th percentile participant, respectively).

The PK after the fixed dosing of efgartigimod PH20 SC was also compared to the weight-based dosing of efgartigimod IV. Efgartigimod C_{trough} observed in participants with gMG in study ARGX-113-2001 and $AUC_{0\text{-}168h}$ observed in healthy participants in study ARGX-113-1907 after 4-weekly administrations of efgartigimod PH20 SC 1000 mg and efgartigimod IV 10 mg/kg were evaluated in function of body weight (Figure 22). Despite the limited weight range in study ARGX-113-1907, similar trends for $AUC_{0\text{-}168h}$ as for C_{trough} in study ARGX-113-2001 were observed. After administration of efgartigimod PH20 SC 1000 mg, there was a trend toward a decrease in efgartigimod exposure with increasing body weight while after administration of efgartigimod IV 10 mg/kg, the opposite trend was observed.

Figure 22: Efgartigimod Ctrough and AUC0-168h After the Fourth Weekly Administration of Efgartigimod PH20 SC 1000 mg or Efgartigimod IV 10 mg/kg as Function of Body Weight in Study ARGX-113-2001 and Study ARGX-113-1907

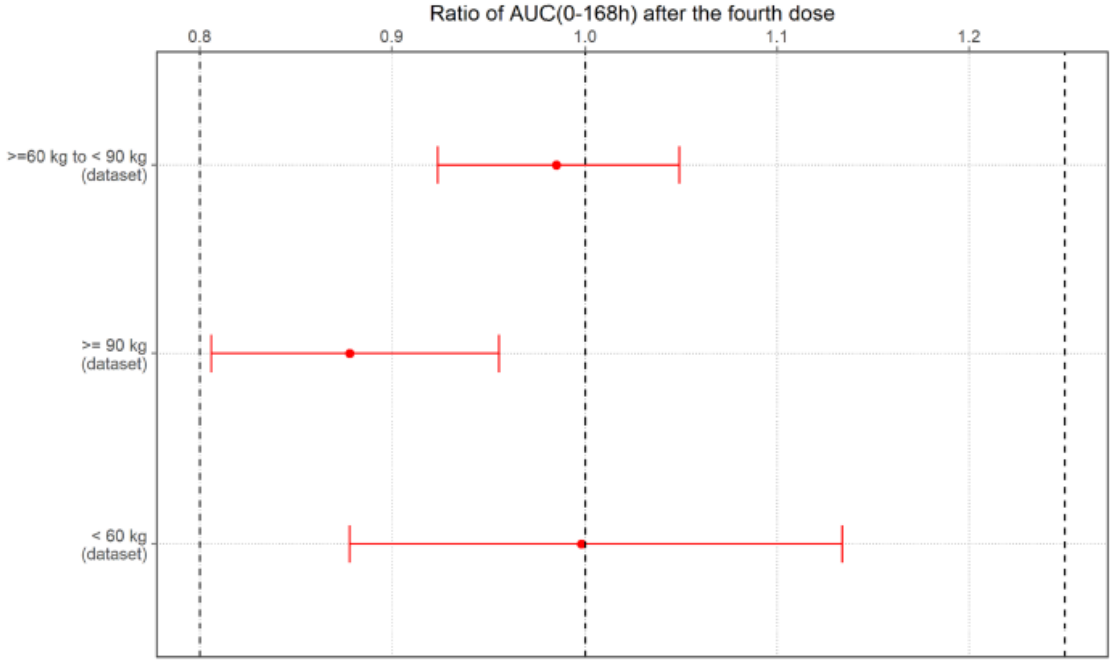




$AUC_{0\text{-}168h}$= area under the concentration-time curve from time 0 up to 168 hours; EFG=efgartigimod; IV=intravenous; SC=subcutaneous Note: $AUC_{0\text{-}168h}$ after the fourth administration of efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg). Loess smoother with 95% confidence intervals

Individual efgartigimod AUC0-168h after the fourth dose of efgartigimod PH20 SC 1000 mg and efgartigimod IV 10 mg/kg were predicted based on the post hoc estimates of the population PK model. Efgartigimod AUC0-168h was investigated for 3 body weight groups: <60 kg, ≥60 kg to <90 kg, and ≥90 kg. Geometric mean ratios and 90% CI for AUC0-168h after administration of efgartigimod PH20 SC 1000 mg in a specific body weight group were calculated using administration of efgartigimod IV 10 mg/kg in participants with body weights ≥60 kg and <90 kg as a reference. The forest plot shows that the AUC0-168h was consistent across the different body weight groups after administration of efgartigimod PH20 SC 1000 mg. The 90% CI of the GMRs all fell within the bioequivalence limits of 0.8 to 1.25 and are not clinically relevant (Figure 23).

Figure 23: Evaluation of the Effect of Body Weight on Simulated Efgartigimod Exposure (AUC_{0-168h})



AUC_{0-168h}= area under the concentration-time curve from time 0 up to 168 hours; CI=confidence interval; IV=intravenous; SC=subcutaneous
Notes: The ratio of AUC_{0-168h} after the fourth weekly administration is based on the original dataset. Efgartigimod IV 10 mg/kg for a body weight of ≥60 kg and <90 kg was used as a reference. Dot=median of AUC_{0-168h}.

Vertical solid lines=90% CI of the AUC_{0-168h} ratio. Vertical dashed lines=reference ratios of 0.8, 1.0 and 1.25

The influence of body weight (using the standard BE limits of 80-125%) on efgartigimod exposure after administration of the fixed dose of efgartigimod PH20 SC 1000 mg was limited and comparable to the exposure observed after administration of weight-based dosing of efgartigimod IV 10 mg/kg.

Race

Of the 55 participants with gMG included in study ARGX-113-2001 receiving efgartigimod PH20 SC, the most common race category was white (90.9%). All Asian participants were Japanese (7.3%). The effect of race and ethnicity on efgartigimod PK and PD was assessed in the population PK/PD analysis. Race and ethnicity were not found to influence any of the model parameters of the final population PK/PD model.

Age

The median (min, max) age for participants with gMG receiving efgartigimod PH20 SC in study ARGX-113-2001 was 53 (19, 84), with the majority of patients (78.2%) in the 18 to <65 years age category. The effect of age on efgartigimod PK and PD was assessed in the population PK/PD analysis. Age was not found to influence any of the model parameters of the final population PK/PD model.

An overview of the elderly subjects who received at least one injection of efgartigimod PH20 SC is provided below.

Table 6: Overview of the elderly population with available PK data included in the clinical development program of efgartigimod PH20 SC

	Age 65-74 (Older Subjects Number / Total Number)	Age 75-84 (Older Subjects Number / Total Number)	Age 85+ (Older Subjects Number / Total Number)
Healthy participants			
ARGX-113-1901	(7 / 32)	(0 / 32)	(0 / 32)
ARGX-113-1907	(1 / 26)	(0 / 26)	(0 / 26)
Participants with gMG			
ARGX-113-2001	(10 / 55)	(2 / 55)	(0 / 55)
ARGX-113-2002[a,b]	(18 / 113)	(6 / 113)	(0 / 113)
Overall	**(36 / 226)**	**(8 / 226)**	**(0 / 226)**

gMG=generalized myasthenia gravis; SC=Subcutaneous
a Number of subjects receiving at least 1 dose of efgartigimod PH20 SC.
b Number of subjects who did not receive of efgartigimod PH20 SC in antecedent study ARGX-113-2001
Overall, the PK in special populations receiving the SC regimen is comparable to the PK after IV administration.

Pharmacokinetic interaction studies

No clinical drug-drug interaction (DDI) studies have been conducted. The effect of concomitant MG treatment of steroids and/or NSIDs was evaluated by means of covariate testing in the population PK/PD analysis. Participants with gMG on steroids (with or without NSIDs), appeared to have 13.6% lower baseline levels of total IgG, this is not considered to be clinically relevant.

Due to its mode of action, efgartigimod is expected to 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 but not IgA, IgD, IgE, or IgM.

Immunogenicity

In the pivotal study in participants with gMG, ARGX-113-2001, the incidence of ADA against efgartigimod was 34.5% in the efgartigimod PH20 SC arm and 20.0% in the efgartigimod IV arm. Neutralizing antibodies against efgartigimod were detected in 3.6% of the participants in each arm. The incidence of antibodies against rHuPH20 was 5.5% and no NAb against rHuPH20 were detected. Efgartigimod SC is considered moderate to highly immunogenic but no sign of an impact of ADAs on the PK of efgartigimod has been observed.

2.5.2.2. Pharmacodynamics

The PD and the PK-PD (exposure-response) relationship of efgartigimod PH20 SC has been studied in both healthy participants and patients with gMG. The primary PD endpoint in studies ARGX-113-1907 (healthy

subjects) and ARGX-113-2001 (patients with gMG) was the percent reduction from baseline in total IgG levels at day 29 (ie, week 4, 7 days after the fourth IV or SC administration) at the noninferiority margin of 10%. The secondary PD endpoints investigated were IgG1, IgG2, IgG3, IgG4, and AChR-Ab. Compared to the gMG IV submission, no additional data on anti-muscle-specific receptor tyrosine kinase (MuSK) antibodies became available.

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

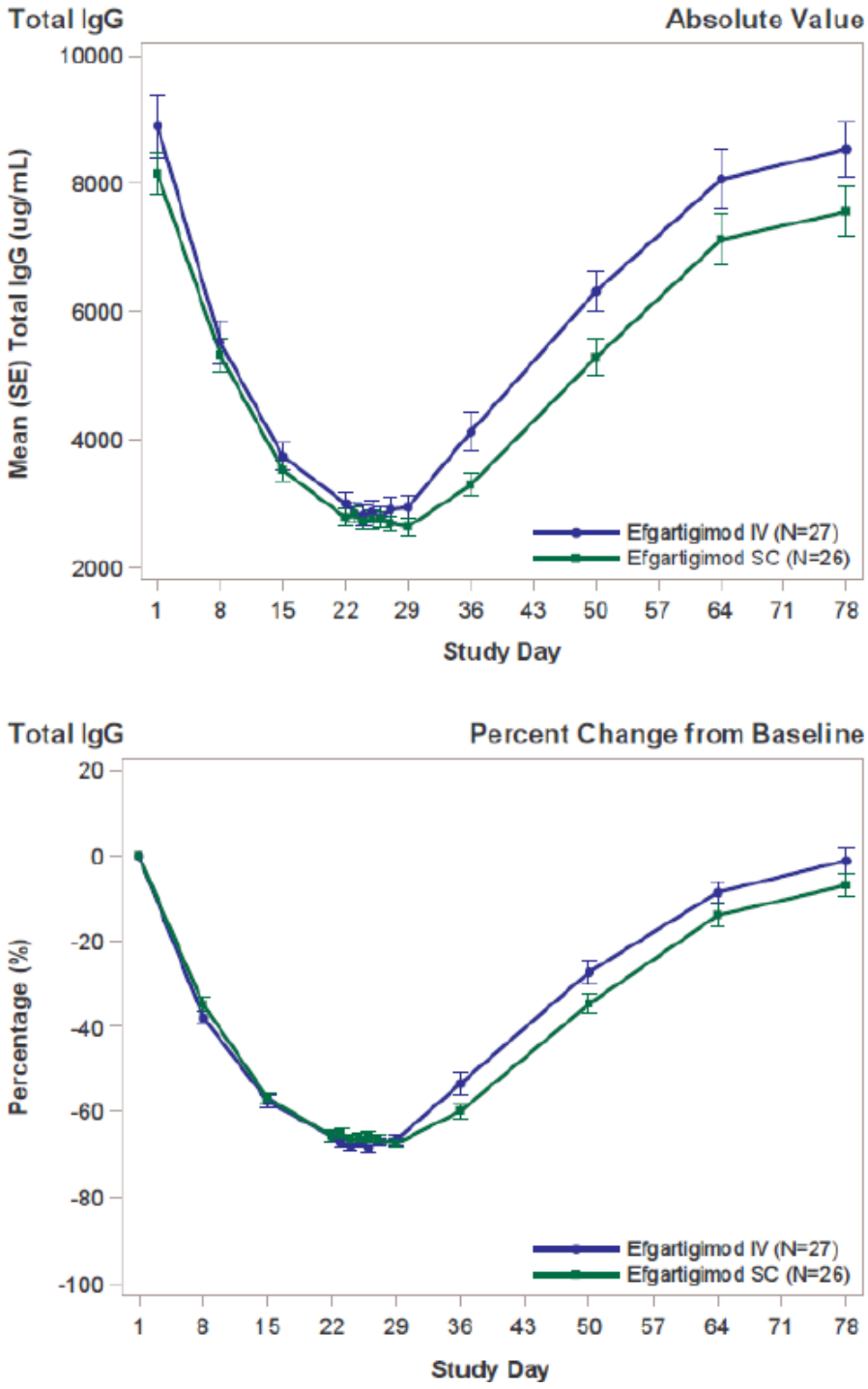
Healthy subjects

Study ARGX-113-1907

This was a phase 1, randomized, open-label, parallel-group study to compare the pharmacodynamics, pharmacokinetics, safety, and tolerability of 4 once-weekly intravenous infusions of efgartigimod 10 mg/kg with 4 once-weekly subcutaneous injections of efgartigimod PH20 1000 mg in healthy subjects. A total of 54 male and female subjects were randomized and dosed in a 1:1 ratio.

Based on the analysis of covariance (ANCOVA) of the primary endpoint, efgartigimod PH20 SC was noninferior to efgartigimod IV in total IgG level reduction at day 29 at the noninferiority margin of 10%. After 4 weekly administrations of efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg, the pattern of total IgG change was comparable between both treatment groups. The absolute values of total IgG and percentage changes from baseline in IgG levels over time for the efgartigimod PH20 SC and efgartigimod IV groups are presented in the below figure. In general, the IgG subtypes (IgG1, IgG2, IgG3 and IgG4) revealed a similar reduction pattern over time.

Figure 24: Mean absolute and mean percentage change from baseline in total IgG over time in healthy participants



IgG=immunoglobulin G; IV=intravenous; SC=subcutaneous; SE=standard error

Mean total IgG levels at baseline, as well at the time of maximum reduction were comparable between both treatment groups. The derived total IgG parameters were comparable between both treatments. For the IgG subtypes, a similar trend as for total IgG was observed. The pattern of total IgG and IgG subtype reduction

was comparable between both treatment groups. Nearly identical ranges of individual time to E_{max} (tE_{max}) values were observed. A summary of the PD parameters is presented below.

Table 7: Summary of Total IgG Parameters after 4 once-weekly administrations of efgartigimod PH20 SC 1000mg or Efgartigimod 10mg/kg in healthy participants

	Efgartigimod PH20 SC 1000 mg		Efgartigimod IV 10 mg/kg	
	n	Mean (SE)	n	Mean (SE)
Baseline (µg/mL)	26	8152 (330)	27	8898 (498)
Reduction at day 29 (%)	25	67.5 (5.5)	26	66.7 (6.5)
E_{max} (%)	25	69.9 (1.10)	26	70.7 (0.853)
TE_{max} (days)	25	24.00 (20.99-28.16)	26	23.50 (20.96-28.13)
$AUEC_{3-4w}$ (%.days)	25	464 (7.66)	26	473 (6.35)
$AUEC_{0-4w}$ (%.days)	25	1340 (31.2)	26	1381 (21.7)
AUEC (%.days)	25	2575 (107)	26	2654 (118)

AUEC=area under the effect curve for percentage reduction compared with baseline over the entire study period (ie, 11 weeks); AUECx-yw=area under the effect curve for percentage reduction compared with baseline over the interval week x to y; E_{max}=maximum percentage reduction compared with baseline; IgG=immunoglobulin G; IV=intravenous; max=maximum; min=minimum; n=number of participants for whom the observation was reported; SC=subcutaneous; SE=standard error; TE_{max}=time to Emax Note: Values are arithmetic means (SE) except median (min-max) for TE_{max}.

Patients with gMG

Study ARGX-113-2001

This was a randomized, open-label, parallel-group, multicenter study in participants with gMG. Eligible participants were AChR-Ab seropositive or seronegative. A total of 111 participants were enrolled and randomized in a 1:1 ratio to receive either efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg once weekly for 4 administrations.

The primary PD endpoint in study ARGX-113-2001 was the percent reduction from baseline in total IgG levels at day 29 (ie, week 4, 7 days after the fourth administration) in the overall population (ie, AChR-Ab seropositive and AChR-Ab seronegative participants with gMG). The primary endpoint of ARGX-113-2001 was met. Total IgG reduction at day 29 in participants with gMG who received efgartigimod PH20 SC1000 mg was noninferior to that in participants who received efgartigimod IV 10 mg/kg after 1 treatment cycle of 4 weekly administrations (noninferiority margin of 10%). The least-squares mean estimate of the percent change from baseline in total IgG level at day 29 was -66.4% (95% CI: -68.91% to -63.86%) in the efgartigimod PH20 SC arm and -62.2% (95% CI: -64.66% to -59.71%) in the efgartigimod IV arm. The corresponding least-squares mean difference in the percent change from baseline in total IgG levels at day 29 between the 2 arms (efgartigimod IV vs efgartigimod PH20 SC) was -4.2% (95% CI: -7.73% to -0.66%). Thus, the upper limit of the CI (-0.66%) was below the prespecified non-inferiority margin of 10% (below table).

The results were consistent when the ANCOVA analysis was repeated for total IgG in the AChR-Ab seropositive population.

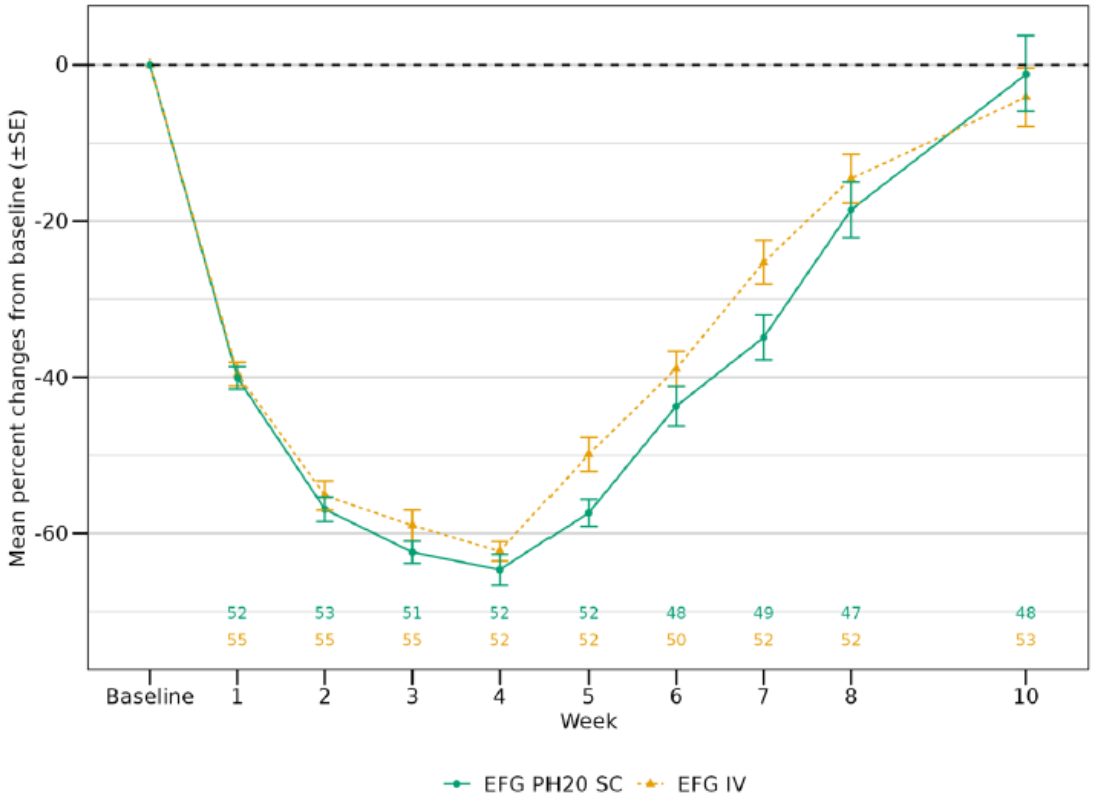
Table 8: ANCOVA Analysis of Percent Change From Baseline in Total IgG at Day 29

EFG PH20 SC			EFG IV			EFG PH20 SC vs EFG IV		
N	LS mean	95% CI	N	LS mean	95% CI	LS of mean difference	95% CI	p-value
Overall population (mITT)								
50	-66.4	-68.91, -63.86	52	-62.2	-64.67, -59.72	-4.2	-7.73, -0.66	<0.0001
AChR-Ab seropositive participants (mITT)								
41	-66.9	-69.78, -64.02	43	-62.4	-65.22, -59.59	-4.5	-8.53, -0.46	<0.0001

AChR-Ab=acetylcholine receptor antibody; ANCOVA=analysis of covariance; CI=confidence interval; EFG=efgartigimod; IgG=immunoglobulin G; IV=intravenous; LS=least squares; mITT=modified intent-to-treatment analysis set; N=number of participants per arm that were included in the ANCOVA analysis; SC=subcutaneous Note: ANCOVA analysis included randomized treatment as a factor and baseline total IgG level as a covariate. There were 5 participants in the efgartigimod PH20 SC arm and 3 participants in the efgartigimod IV arm who were excluded from the mITT analysis set because IgG data were unavailable at day 29

The percent change from baseline in total IgG levels over time for the overall population is summarized in the below figure and table.

Figure 25: Percent Change From Baseline in Total IgG Level Over Time in the Overall Population



AChR-Ab=anti-acetylcholine receptor antibody; EFG=efgartigimod; IgG=immunoglobulin G; IV=intravenous; SC=subcutaneous; SE=standard error Note: Assessments after receiving immunoglobulin-related MG therapy or plasmapheresis procedure were excluded

Table 9: Summary of Total IgG Parameters After 4 Once-Weekly Administrations of Efgartigimod PH20 SC 1000 mg or Efgartigimod IV 10 mg/kg in Participants with gMG (Overall Population)

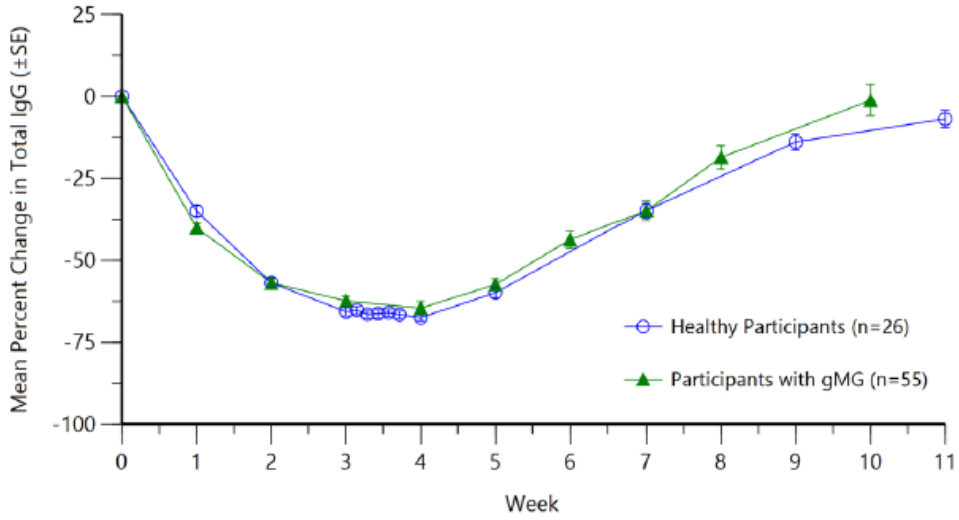
	Efgartigimod PH20 SC 1000 mg		Efgartigimod IV 10 mg/kg		GMR (90% CI)
	n	Mean (SE)	n	Mean (SE)	
Baseline (µg/mL)	55	8747 (495)	55	8995 (472)	NA
Reduction at day 29 (%)	52	64.6 (1.98)	52	62.3 (1.24)	1.03 (0.95–1.12)
E_{max} (%)	55	67.0 (1.91)	55	63.6 (1.58)	1.10 (0.96–1.25)
$AUEC_{0-1w}$ (%.days)	52	139 (5.48)	55	139 (5.67)	0.97 (0.87–1.07)
$AUEC_{3-4w}$ (%.days)	49	447 (9.43)	52	427 (9.76)	1.06 (0.99–1.12)
$AUEC_{0-4w}$ (%.days)	51	1333 (30.8)	52	1312 (26.4)	1.02 (0.96–1.08)
$AUEC_{0-8w}$ (%.days)	45	2607 (81.8)	50	2386 (79.2)	1.06 (0.98–1.14)
AUEC (%.days)	47	2791 (130)	51	2506 (118)	1.03 (0.92–1.17)

AUEC=area under the effect curve for percentage reduction compared with baseline over the entire study period; AUECx-yw=AUEC over the interval week x to y; CI=confidence interval; GMR=geometric mean ratio; Emax=maximum percentage reduction compared with baseline; IgG=immunoglobulin G; IV=intravenous; n=number of participants for whom the observation was reported; NA=not applicable; SC=subcutaneous; SE=standard error Note: Assessments after receiving immunoglobulin-related MG therapy or plasmapheresis procedure were excluded

Healthy subjects versus patients with gMG

After administration of 4 weekly injections of efgartigimod PH20 SC 1000 mg, the pattern of total IgG reduction was similar in healthy subjects and patients with gMG (figure below).

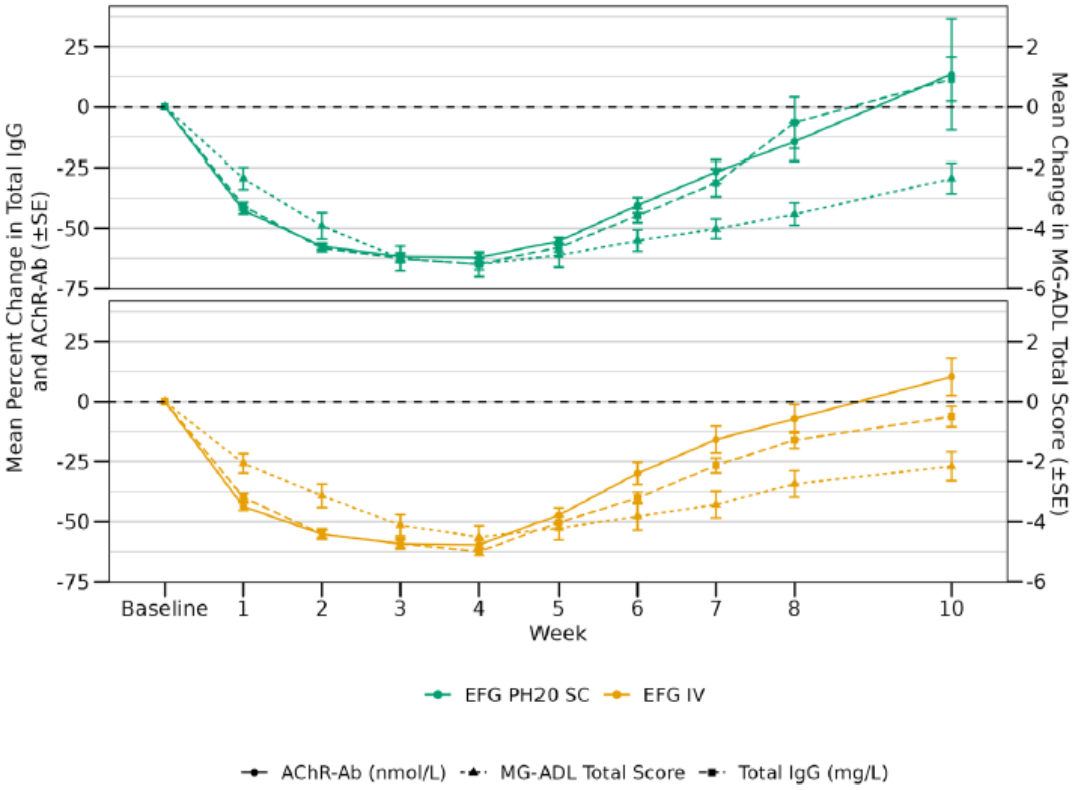
Figure 26: Mean percent change from baseline in total IgG after four weekly injections of Efgartigimod PH20 1000mg in Healthy participants and participants with gMG.



gMG=generalized myasthenia gravis; IgG=immunoglobulin G; n=number of observations; SC=subcutaneous; SE=standard error
NOTE: Doses were administered at week 0, week 1, week 2 and week 3. Assessments after receiving immunoglobulin-related MG therapy or plasmapheresis procedure were excluded.

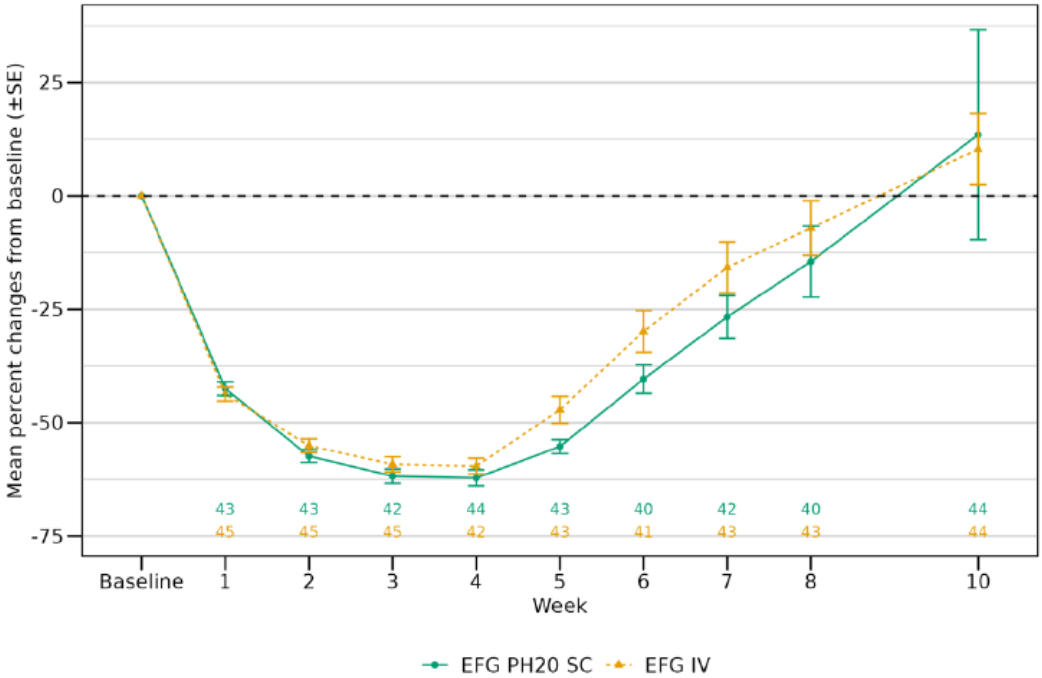
In study 2001, a clear correlation between decline in total IgG and AChR-Ab levels in the seropositive population was demonstrated (Figure 27). The reduction in AChR-Ab from baseline is similar between SC and IV administration of efgartigimod (Figure 28).

Figure 27: Change in MG-ADL Total Score and Percent Change in Levels of Total IgG and AChR-Ab in AChR-Ab Seropositive Population in Study ARGX-113-2001



AChR-Ab=anti acetylcholine receptor antibody; EFG=efgartigimod; IgG =immunoglobulin G; IV=intravenous; MG-ADL=Myasthenia Gravis Activities of Daily Living; SC=subcutaneous; SE=standard error

Figure 28: Percent Change From Baseline in AChR-Ab Levels Over Time in the AChR-Ab Seropositive Population



AChR-Ab=anti acetylcholine receptor antibody; EFG=efgartigimod; IgG =immunoglobulin G; IV=intravenous; SC=subcutaneous; SE=standard error

Intersubject variability in PD

The intersubject variability on total IgG levels during the first cycle of 4 weekly administrations of efgartigimod PH20 SC 1000 mg in the phase 3 study ARGX-113-2001 was moderate to high with %CV over time ranging from 38.8% to 53.3%.

The intersubject variability on absolute AChR-Ab levels was high with %CV over time ranging from 203.5% to 274.9%. A large variability in baseline AChR-Ab data was observed (%CV=503%).

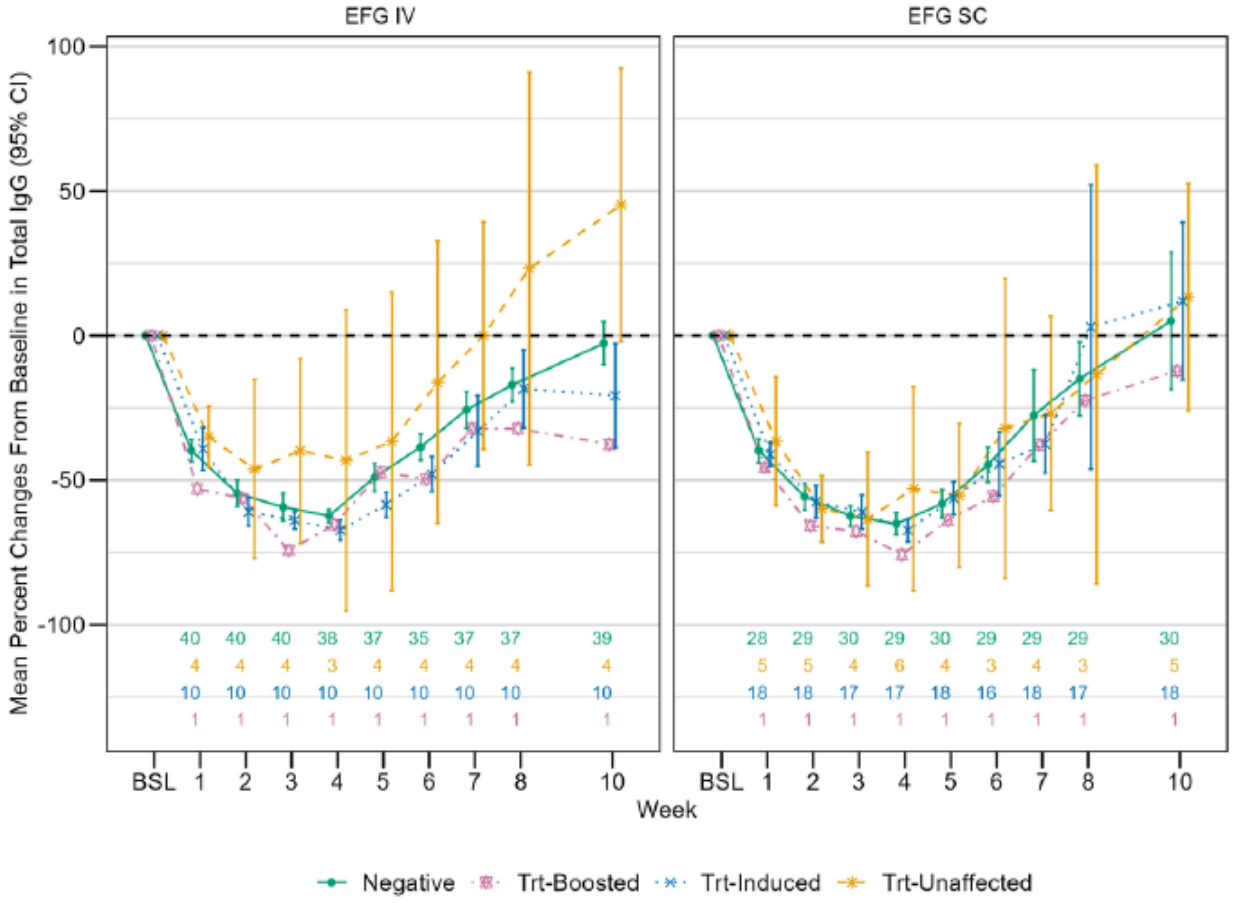
AChR-Ab serotype

The AChR-Ab serotype had no effect on the PD of efgartigimod PH20 SC. Levels of total IgG in AChR-Ab seropositive and AChR-Ab seronegative participants were reduced to a similar extent.

Impact of ADA on PD

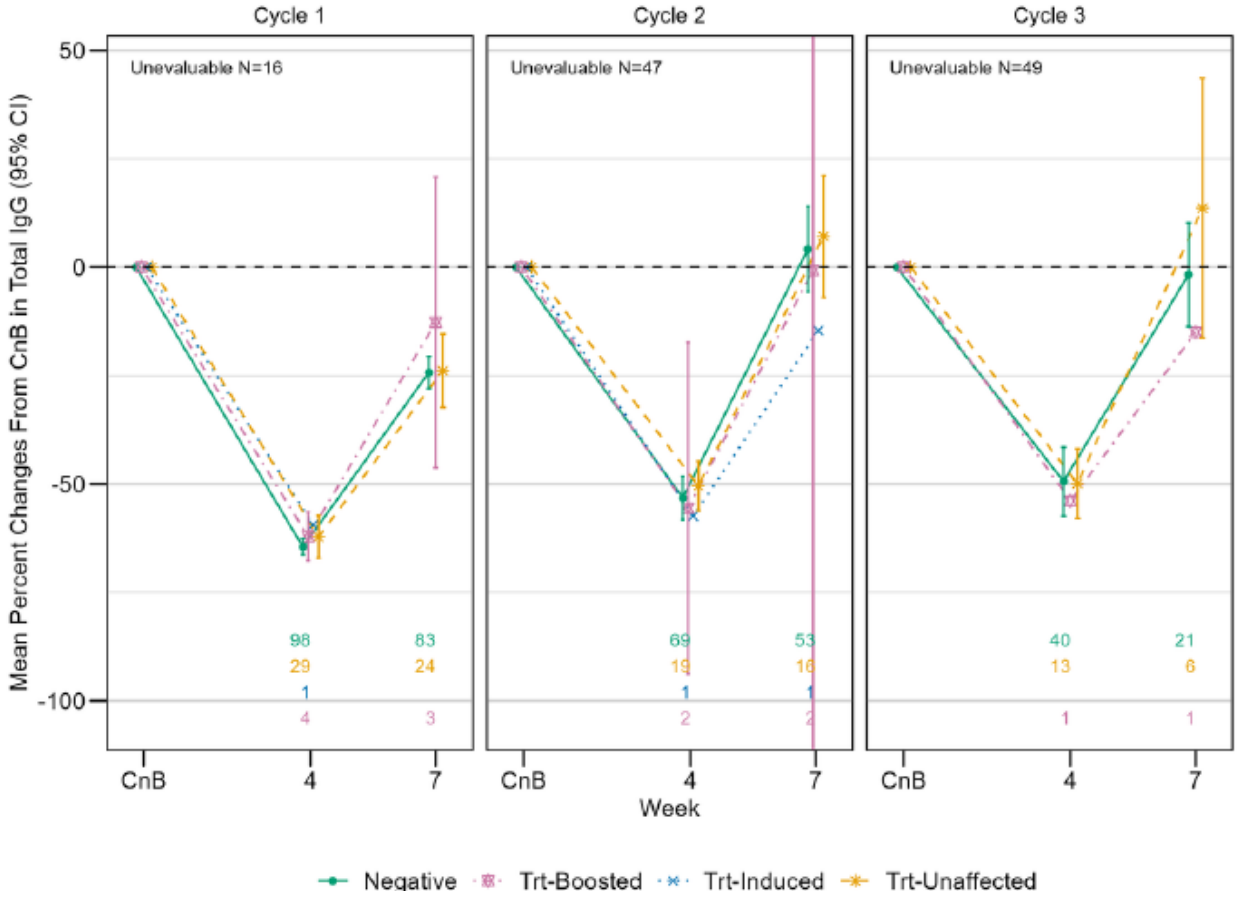
There was no meaningful difference in the percent change from cycle baseline in total IgG levels (PD) across the cycles between participants negative for ADA against efgartigimod when compared with participants with treatment-induced, treatment-boosted, or treatment-unaffected ADA against efgartigimod (figures below).

Figure 29: Mean percent change from baseline in total IgG levels (95% CI) by participant classification of ADA against efgartigimod in ARGX-113-2001



ADA=Antidrug antibody(ies); BSL=baseline; CI=Confidence interval; EFG= efgartigimod; IgG=immunoglobulin gamma; IV=intravenous; SC=subcutaneous; Trt=treatment
All ADA categories are represented
Total number of participants per ADA classification are indicated at the bottom of the graphs for each time point, color-coded to align with the figure legend.

Figure 30: Mean percent change from cycle baseline in total IgG levels (95%CI) by cycle participant classification of ADA against efgartigimod in ARGX-113-2002



ADA=Antidrug antibody(ies): CI=Confidence interval: CnB=cycle n baseline; IgG=immunoglobulin gamma; Trt=treatment
All ADA categories are represented
Total number of participants per category are indicated at the bottom of the graphs for each time point, color-coded to align with the figure legend.

Exposure-response analyses

Exposure-efficacy

The number (%) of MG-ADL responders in ARGX-113-2001 for the overall and AChR-Ab seropositive population in the efgartigimod PH20 SC treatment group by C_{trough} and $AUC_{0\text{-}168h}$ quartiles is presented in the table below.

Table 10: MG-ADL response by quartiles of Ctrough and AUC 0-168h in the Efgartigimod PH20 SC Group

	Quartile	Number of MG-ADL responders (%)	
		C_{trough} Quartiles[a]	AUC_{0-168h} Quartiles[b]
Overall	Q1	10 / 14 (71.4)	8 / 14 (57.1)
	Q2	9 / 11 (81.8)	11 / 14 (78.6)
	Q3	7 / 12 (58.3)	9 / 14 (64.3)
	Q4	10 / 12 (83.3)	10 / 13 (76.9)
AChR-Ab seropositive	Q1	8 / 10 (80.0)	7 / 12 (58.3)
	Q2	9 / 10 (90.0)	9 / 11 (81.8)
	Q3	5 / 10 (50.0)	7 / 11 (63.6)
	Q4	9 / 10 (90.0)	9 / 11 (81.8)

AChR-Ab=anti=acetylcholine receptor antibody(ies); AUC_{0-168h}=are under the concentration-time curve from time 0 up to 168 hours; Ctrough=observed through concentration at week 4; MG-ADL=Myasthenia Gravis activities of daily living; Qn=quartile number; CS=subcutaneous
A Quartile cutoff values (25th, 50th, and 75th percentile) for C_{trough} were 16.6, 19.8, and 25.1 ug/mL and 16.6 20.2 and 25.3 ug/mL in overall and Ach-Ab seropositive population, respectively.
B Quartile cutoff values (25th, 50th, and 75th percentile) for AUC_{0-168h} were 4995, 5843, and 6423 ug.h/mL and 5006, 5854, and 6423 ug.h/mL in overall and Ach-Ab seropositive population, respectively.

Exposure-safety

An overview of the treatment-emergent adverse events (TEAEs) in study ARGX-113-2001 by C_{trough} and AUC_{0-168h} quartiles in the efgartigimod PH20 SC treatment group are presented in the below tables.

Table 11: Overview of TEAEs in the Efgartigimod PH20 SC Group by quartiles of Ctrough at week 4 (safety analysis set)

	Q1 (N=14)		Q2 (N=11)		Q3 (N=12)		Q4 (N=12)		Missing[d] (N=6)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall										
≥1 TEAE	10 (71.4)	36	6 (54.5)	16	9 (75.0)	19	8 (66.7)	42	4 (66.7)	20
≥1 Serious TEAE	3 (21.4)	3	0	-	1 (8.3)	1	2 (16.7)	4	2 (33.3)	2
≥1 TEAE of CTCAE severity grade ≥3	3 (21.4)	3	0	-	1 (8.3)	1	3 (25.0)	4	2 (33.3)	3
≥1 Fatal TEAE	0	-	0	-	0	-	0	-	0	-
≥1 Treatment-related TEAE according to PI	7 (50.0)	15	5 (45.5)	9	4 (33.3)	7	5 (41.7)	13	3 (50.0)	8
≥1 Serious treatment-related TEAE	0	-	0	-	0	-	0	-	0	-
≥1 TEAE leading to interruption of IMP	1 (7.1)	1	0	-	0	-	0	-	0	-
≥1 TEAE leading to discontinuation of IMP	0	-	0	-	0	-	0	-	2 (33.3)	2
≥1 AESI[a]	1 (7.1)	1	1 (9.1)	1	3 (25.0)	3	2 (16.7)	2	3 (50.0)	3
≥1 IRR[b]	6 (42.9)	10	3 (27.3)	4	2 (16.7)	2	2 (16.7)	3	1 (16.7)	1
≥1 ISR (localized)[c]	8 (57.1)	16	5 (45.5)	9	2 (16.7)	3	3 (25.0)	5	3 (50.0)	6

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; C_{trough}=observed trough concentration at week 4; IMP=investigational medicinal product; IRR=injection-related reaction; ISR=injection site reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PI=principal investigator; PT=Preferred Term; Qn=quartile number; SMQ=standardized MedDRA query; SOC=System Organ Class; TEAE=treatment-emergent adverse event

[a] An AESI was defined as any TEAE in the MedDRA SOC infections and infestations.

[b] IRRs 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.

[c] Localized ISRs were defined as adverse events with MedDRA high level term 'Injection site reactions' regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized injection site reactions and the abovementioned SMQs for the injection- or infusion-related reactions.

[d] For 6 participants with TEAE, C_{trough} at week 4 was missing or measured outside the pre-specified window.

Note: Quartile cut-off values (25th, 50th and 75th percentile) for C_{trpugh} were 16.6, 19.8, and 25.1 µg/mL
The denominator for the percentage calculations is N: the total number of patients in the safety analysis set per treatment and per quartile group.

Table 12: Overview of TEAEs in the Efgartigimod PH20 SC Group by quartiles of AUC0-168h at week 4 (safety analysis set)

	Q1 (N=14)		Q2 (N=14)		Q3 (N=14)		Q4 (N=13)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall								
≥1 TEAE	11 (78.6)	46	10 (71.4)	25	5 (35.7)	19	11 (84.6)	43
≥1 Serious TEAE	4 (28.6)	4	0	-	1 (7.1)	1	3 (23.1)	5
≥1 TEAE of CTCAE severity grade ≥3	4 (28.6)	5	0	-	1 (7.1)	1	4 (30.8)	5
≥1 Fatal TEAE	0	-	0	-	0	-	0	-
≥1 Treatment-related TEAE according to PI	8 (57.1)	20	9 (64.3)	14	3 (21.4)	11	4 (30.8)	7
≥1 Serious treatment-related TEAE	0	-	0	-	0	-	0	-
≥1 TEAE leading to interruption of IMP	1 (7.1)	1	0	-	0	-	0	-
≥1 TEAE leading to discontinuation of IMP	2 (14.3)	2	0	-	0	-	0	-
≥1 AESI[d]	3 (21.4)	3	2 (14.3)	2	2 (14.3)	2	3 (23.1)	3
≥1 IRR[e]	5 (35.7)	7	6 (42.9)	9	2 (14.3)	3	1 (7.7)	1
≥1 ISR (localized)[f]	9 (64.3)	18	8 (57.1)	14	2 (14.3)	4	2 (15.4)	3

Source: Module 5.3.5.1, ARGX-113-2001 EMA output, Table 14.3.1.1.c

AE=adverse event; AESI=adverse event of special interest; AUC_{0-168h}=area under the concentration-time curve from time 0 up to 168 hours; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IRR=injection-related reaction; ISR=injection site reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PI=principal investigator; PT=Preferred Term; Qn=quartile number; SMQ=standardized MedDRA queries; SOC=System Organ Class; TEAE=treatment-emergent adverse event

[a] An AESI was defined as any TEAE in the MedDRA SOC Infections and infestations.

[b] IRRs 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.

[c] Localized ISRs were defined as adverse events with MedDRA high level term 'Injection site reactions' regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized injection site reactions and the abovementioned SMQs for the injection- or infusion-related reactions.

Note: Quartile cut-off values (25th, 50th and 75th percentile) for AUC_{0-168h} were 4995, 5843, and 6423 µg.h/mL
The denominator for the percentage calculations is N: the total number of patients in the safety analysis set per treatment and per quartile group.

2.5.3. Discussion on clinical pharmacology

The MAH has been granted a marketing authorisation for efgartigimod as an IV product, and the present line extension concerns a fixed dose of 1000 mg efgartigimod coformulated with the permeation enhancer rHuPH20 (2000 U/mL) for SC administration. The proposed posology is 1000 mg efgartigimod once weekly for four weeks with subsequent treatment cycles according to clinical evaluation, the same administration regimen as with IV administration.

The clinical pharmacology program for the SC application assessed the PK, PD, and immunogenicity of efgartigimod administered SC (or IV for comparison) in two phase 1 studies in healthy subjects (ARGX-113-1901 and ARGX-113-1907) and in two phase 3 studies in patients with gMG (ARGX-113-2001 and ARGX-113-2002). The aim of the fixed SC dose regimen was to find a dose resulting in a similar PD effect as achieved with the treatment cycle of efgartigimod IV 10 mg/kg. Based on the similar effects on IgG, AChR-Ab, and MG-ADL the selected dose for SC administration seems to be acceptable.

A sandwich immunoassay on the Gyrolab Bioaffy system was validated for quantification of efgartigimod in Study 2001. This method was cross validated with an older ELISA method. Cross-validation results indicated

the ELISA method gave 38.5% lower results for concentrations <10 µg/mL than the Gyrolab method and it seemed only study samples were affected, not spiked samples. This could indicate the older method and thus the drug quantification in earlier studies e.g., Study 1907 and 1901 was impacted by the matrix of study samples (maybe ADA formation). A validated immunoassay method for measurement of IgG subtypes (IgG1, IgG2, IgG3, IgG4), IgA, and IgM was also submitted with this extension. The efgartigimod ADA assay (an ACE-bridging ELISA) was re-validated and submitted with this extension after substantial changes were made to the assay. Drug tolerance at 100 ng/mL ADA PC level was improved from 5.66 µg/mL to 30.9 µg/mL (screening assay) and to at least 100 µg/mL (confirmatory assay) efgartigimod. The updated method was applied in Study 2001 and 2002, while the old method with limited drug tolerance was applied in Study 1702, 1907 and 1901. There is no quantitation method for rHuPH20 as it is not systemically detectable. Validated methods were used for screening, confirmation and titration of anti-rHuPH20 antibodies and for detection of NAbs to rHuPH20. The MAH commits to submit the final bioanalytical reports covering data from extension study ARGX-113-2002 upon study finalisation **(REC)**.

The popPK model for efgartigimod PH20 SC was based on a 3-compartment PK model submitted for the approved IV treatment and containing the assumption that V2 = V3 while IIV was included on CL, V1, V2/V3, Ka and covariance between CLxV1. Data from Study 2001 was included in model development. The final PopPK model could predict the data in Study 2001 and in Study 2002 (data cut-off 12 Jan 2021, external fit). An indirect response model including data from studies 1501, 1602, 1702, 1704, 1901 and 1907 was updated with data from Study 2001 to describe the PK/total IgG relation of efgartigimod. Individual total IgG observations from Study 2001 indicated the proposed SC dosing can lead to a better IgG response than observed after IV treatment. The existing PK/total IgG/binding AChRAb model based on the final PK/total IgG model and AChRAb data collected in seropositive and in seronegative gMG patients from IV studies 1602 (n=12) and 1704 (n=84), was updated with AChRAb data collected in seropositive patients from Study 2001. Covariate effects were all fixed and came from the final PK/total IgG model and were thus related to the total IgG data. A bounded integer model for MG-ADL score with data from studies 1602, 1704 and 1705 (all IV dosed) was updated with MG-ADL score from study 2001. The final PK/total lgG/binding AChRAb model was used to predict the binding AChRAb concentrations as a measure of drug effect at the time-points for MG-ADL scoring, however, the model was based on a dataset that included both AChRAb seropositive (n=220) and seronegative patients (n=57). The MAH considers that the submitted MG-ADL total score model based on the overall population is suitable for clinical effect simulations and is adequately reflecting the AChR-Ab seropositive population receiving the efgartigimod PH20 SC treatment. Following a model update by exclusion of data from seronegative patients, the drug effect parameter α changed from −0.262 to −0.301 with overlapping 95%CIs. It is agreed that excluding the data from AChR-Ab seronegative patients did not change the parameter estimates of the final MG-ADL Score model much nor resulted in a better fit as judged from VPCs. However, to predict AChR-Ab levels in seronegative patients in order to include data from this sub-group of patients is not considered adequate. The MAH argues that these predicted levels may represent unknown autoantibodies. Data from the AChR-Ab seronegative patient population just introduce bias and should not be included in the PD population. Due to performance similarities of the two models, the simulations made within this procedure are accepted for this procedure only. For future applications, however, inclusion of data from AChR-Ab seronegative patients in the PD/efficacy models for seropositive patients will not be accepted.

In gMG patients, the observed exposure in terms of C_{trough} is slightly higher (approximately 50%) in the SC arm compared with the IV arm, while AUC is comparable. C_{trough} was similar between AChR-Ab seropositive and seronegative patients. Based on popPK modelling, the estimated bioavailability of efgartigimod SC is 76.5%. The PK results of efgartigimod with or without the absorption enhancer indicate that the absorption is significantly faster with the enhancer but the overall exposure is comparable.

The volume of distribution is 18 L. As expected, the rate of elimination in healthy subjects is similar between IV and SC administered efgartigimod. Further, the elimination rate is not affected by the presence of the absorption enhancer. The accumulation after efgartigimod PH20 SC 1000 mg was minimal, and no time dependency has been demonstrated.

Dose proportionality has not been assessed after multiple SC dosing; this is acceptable. After single SC doses of 750 to 1750 mg efgartigimod, it is agreed that a trend of more than dose-proportional increase in exposure with increasing SC doses cannot be excluded. However, as stated by the Applicant, the analyses are based on little data (n=8 in each dose group), so no conclusion can be made.

Based on popPK data, the variability in disposition PK parameters following the SC regimen is considered moderate. In healthy volunteers, the variability (CV) in C_{max} (42%) and AUC (26%) is high and moderate, respectively.

As for special populations, a combined dataset from healthy participants and participants with gMG receiving efgartigimod IV or efgartigimod PH20 SC, including data from study ARGX-113-2001, was used for the covariate analysis in the population PK/PD model development. The inclusion of SC data has not altered the effects of the special populations on the PK of efgartigimod.

No clinical DDI studies have been conducted. According to the EMA guideline on therapeutic proteins this is acceptable. As informed in the SmPC, due to its mode of action, efgartigimod is expected to 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.

As expected, the incidence of ADAs was higher in the subcutaneous arm than in the IV arm in study 2001. However, no sign of any impact of ADAs on PK, PD, efficacy, or safety of efgartigimod treatment has been reported.

When patients with gMG received 4 once-weekly administrations of either efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg (study 2001), the reduction from baseline in total IgG at day 29, the primary endpoint, was very similar. The mean maximum reduction was slightly higher in the SC group. In healthy subjects receiving IV or SC efgartigimod, the results are very similar.

Based on data from study 1907 and 2001, the reduction in total IgG between healthy subjects and patients receiving SC efgartigimod was very similar.

The AChR-Ab serotype (seropositive or seronegative) had no effect on the PD of efgartigimod PH20 SC.

No data concerning secondary pharmacology have been presented. FcRn promotes transcytosis of IgG into tissues and recycles albumin; however, in the IV application it was reported that there was no reduction in levels of serum albumin with the administration of efgartigimod.

Due to the PD effects of efgartigimod, no QTc study has been conducted. This is acceptable.

ADA does not seem to influence the PD effect on IgG.

Exposure-efficacy and exposure-safety analyses, using MG-ADL and TEAE as response parameters, showed no ER relationships.

2.5.4. Conclusions on clinical pharmacology

The clinical pharmacology of efgartigimod PH20 SC is documented in both healthy participants and patients with gMG. The primary PD endpoint in studies ARGX-113-1907 (healthy subjects) and ARGX-113-2001 (patients with gMG) was the percent reduction from baseline in total IgG levels at day 29. In addition, population PK/PD analyses have been performed. Considering the nature of the product (a therapeutic protein), the pharmacology package is considered adequate and the proposed dosing of efgartigimod seems appropriate. A few PK/PD issues remains to be addressed.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Submission of the final bioanalytical reports covering data from extension study ARGX-113-2002 upon study finalisation

2.5.5. Clinical efficacy

Table 13: Overview of Clinical Studies Supporting the Efgartigimod PH20 SC Application

Study status	Study design	Treatment (number of participants)	Primary objective
Healthy participants			
ARGX-113-1702 Completed	Phase 1, randomized, open-label, parallel-group study of efgartigimod SC (without rHuPH20) and efgartigimod IV	EFG IV 1×10 mg/kg (8) EFG IV 4×10 mg/kg (8) EFG SC 1×10 mg/kg (8) EFG IV 2×20 mg/kg followed by EFG SC 8×300 mg (16)	PK, PD
ARGX-113-1901 Completed	Phase 1, randomized, open-label, parallel-group study of efgartigimod comixed with rHuPH20 (single dosing)	EFG SC 750 mg (8) EFG SC 1250 mg (9) EFG SC 1750 mg (8) EFG SC 10 mg/kg (8)	PD
ARGX-113-1907 Completed	Phase 1, randomized, open-label, parallel-group study of efgartigimod IV and efgartigimod PH20 SC	EFG PH20 SC 1000 mg, 4 weekly administrations (27) EFG IV 10 mg/kg, 4 weekly administrations (27)	PD
Efgartigimod PH20 SC			
ARGX-113-2001 Completed	Phase 3, randomized, open-label, parallel-group study to compare efgartigimod PH20 SC with efgartigimod IV AChR-Ab seropositive and seronegative	EFG PH20 SC 1000 mg (55) EFG IV 10 mg/kg (55) 1 cycle of 4 weekly administrations and 7-week follow-up	PD: total IgG reduction at D29 in the overall population
ARGX-113-2002 Ongoing (IA1; safety data cutoff 02 Mar 2022)	Phase 3, long-term, open-label, study with efgartigimod PH20 SC AChR-Ab seropositive and seronegative	EFG PH20 SC 1000 mg, 4 weekly administrations (164) multiple cycles Retreatment per clinical evaluation if ≥28 days	

Study status	Study design	Treatment (number of participants)	Primary objective
Participants with gMG			
Efgartigimod IV			
ARGX-113-1602 Completed	Phase 2, randomized, double-blinded, placebo-controlled study of efgartigimod IV AChR-Ab seropositive	EFG IV 10 mg/kg (12) placebo (12) 1 cycle of 4 weekly administrations	Safety
ARGX-113-1704 Completed	Phase 3, randomized, double-blinded, placebo-controlled study of efgartigimod IV AChR-Ab seropositive and seronegative	EFG IV 10 mg/kg (84) placebo (83) 1-3 cycles of 4 weekly administrations Retreatment per clinical criteria	MG-ADL responders in AChR-Ab seropositive in cycle 1
ARGX-113-1705 Ongoing (IA4; safety data cutoff 31 Jan 2022)	Phase 3, open-label, follow-on to study ARGX-113-1704 with efgartigimod IV AChR-Ab seropositive and seronegative	EFG IV 10 mg/kg (151) multiple cycles Retreatment first year per clinical criteria; thereafter per clinical evaluation if ≥28 days	Safety

AChR-Ab=anti-acetylcholine receptor antibody; CSR=clinical study report; D=day; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IA=interim analysis; IV=intravenous(ly); EFG=efgartigimod; IgG=immunoglobulin gamma; MG-ADL=Myasthenia Gravis Activities of Daily Living; PD=pharmacodynamic; PK=pharmacokinetic rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

2.5.5.1. Dose-response studies

Dose response is discussed in Clinical Pharmacology section.

2.5.5.2. Main study

Title of study ARGX-113-2001: A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis

Methods

The phase 3 study ARGX-113-2001 was a multicenter, randomized, open-label, parallel-group, 12-week study based on the principle of PD-based bridging from efgartigimod IV to the SC route of administration. The bridging from efgartigimod IV to efgartigimod PH20 SC is done by demonstrating a similar PD effect, as measured by percent reduction from baseline in total IgG levels at day 29 by an NI margin of 10%, and by demonstrating that total IgG reduction was associated with a clinical response in participants with gMG. The selected patient population mirrored the eligibility criteria of the pivotal study of efgartigimod IV 10 mg/kg, ARGX-113-1704.

The overall study duration was approximately 12 weeks (2 weeks screening, 3 weeks treatment (once weekly starting at day 1, baseline), 7 weeks follow-up period)

At the end of the study, eligible participants could roll over into a single-arm, open-label extension study, ARGX-113-2002, to receive efgartigimod PH20 SC.

Methods

- **Study Participants**

Diagnosis and Main Criteria for Study Eligibility:

- Adult participants who were diagnosed with gMG with confirmed documentation and supported by at least 1 of the following:

  – History of abnormal neuromuscular transmission demonstrated by single-fiber electromyography or repetitive nerve stimulation

  – History of positive edrophonium chloride test

  – Demonstrated improvement in MG signs upon treatment with oral acetylcholinesterase (AChE) inhibitors as assessed by the treating physician

- An MG-ADL total score of ≥5 points, with >50% of the total score attributed to non-ocular symptoms, at screening and baseline
- Receiving a stable dose of concomitant therapy for gMG
- Meeting the clinical criteria as defined by the MGFA class II, III, IVa, or IVb.

- **Treatments**

Efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg once weekly for 4 administrations (4 doses on days 1, 8, 15, and 22) during 1 clinical cycle. Efgartigimod was administered concomitantly with a stable dose of the participant's current gMG therapy, which could have included AChE inhibitors, steroids, and NSIDs.

Efgartigimod IV was administered by a 1-hour infusion performed by the site staff.

Efgartigimod PH20 SC was administered at the site by the study staff or by the participant (or their caregiver, as appropriate).

During the study, participants may NOT receive any monoclonal antibody, other experimental/study investigational medical product, live or live-attenuated vaccines, a change in the dose or frequency of their current gMG, a change in concomitant therapy for gMG, PLEX, IVIg, immunoadsorption, or a change in dosage or type of corticosteroid used as a monotherapy or in combination.

PLEX, IVIg, immunoadsorption, or a change in dosage or type of corticosteroid are considered rescue therapy if both of the following conditions apply:

1. The treating physician believes that the participant's health is in jeopardy if rescue therapy is not provided and

2. The participant is deteriorating clinically according to the protocol-defined criteria, which includes at least 1 of the following: a. new or worsening of respiratory/bulbar symptoms or b. at least a 2-point increase in any individual non-ocular items on the MG-ADL scale as compared to the previous visit.

- **Objectives and endpoints**

Objectives	Endpoints
Primary	
• To demonstrate the pharmacodynamic (PD) effect of injections of 1000 mg efgartigimod PH20 SC, administered once weekly for 4 administrations, is NI to IV infusions of efgartigimod at a dose of 10 mg/kg administered once weekly for 4 administrations	• Percent reduction from baseline in total IgG levels at day 29 (ie, 7 days after the fourth IV or SC administration)
Secondary	
• To compare the PD effect of efgartigimod PH20 SC and efgartigimod IV over time	• Absolute values, change from baseline, and percent reduction from baseline in total IgG levels over time • Absolute values, change from baseline, and percent reduction from baseline in anti-acetylcholine receptor antibody (AChR-Ab) levels over time in AChR-Ab seropositive participants • Absolute values, change from baseline, and percent reduction from baseline in IgG subtype levels (IgG1, IgG2, IgG3, and IgG4) over time • Area under the effect curve (AUEC) of the percent reduction from baseline total IgG and similar AUEC for each IgG subtype per dosing interval (days 1-8, days 8-15, days 15-22, and days 22-29), days 1-29, and over the entire study (days 1-71)
• To evaluate the pharmacokinetics (PK) of efgartigimod PH20 SC and efgartigimod IV	• PK parameters: maximum concentration (C_{max}) (after all doses for the IV treatment arm) and concentration observed predose (C_{trough}) (after all doses for the IV and SC treatment arms)
• To evaluate the safety, tolerability, and immunogenicity of efgartigimod PH20 SC and efgartigimod IV	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod • Incidence and prevalence of antibodies against rHuPH20 in the SC treatment arm • Incidence and severity of adverse events (AEs), incidence of serious AEs (SAEs), and changes in laboratory test results, physical examination results, vital signs, and electrocardiogram (ECGs) results
• To evaluate the clinical efficacy of efgartigimod PH20 SC and efgartigimod IV	• Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders • Number and percentage of Quantitative Myasthenia Gravis (QMG) responders • Change from baseline in MG-ADL total score over time • Change from baseline in QMG score over time
Exploratory	
• To evaluate the competency of participants or caregivers to administer efgartigimod PH20 SC	• Number and percentage of participants or caregivers completing the self-administration/caregiver-supported administration training in the SC treatment arm • Number and percentage of participants or caregivers in the SC treatment arm determined by the site staff to be sufficiently competent to administer efgartigimod PH20 SC • Number and percentage of participants or caregivers in the SC treatment arm that administer efgartigimod PH20 SC under site staff supervision

Primary objective and endpoint

The primary objective of this study was to demonstrate the noninferiority (NI) of the SC formulation compared with the IV formulation in treating participants with gMG using total IgG percent reduction at day 29 based on an NI margin of 10%.

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment as a factor and total IgG levels at baseline as a covariate. The NI evaluation was based on a percent reduction from baseline in total IgG levels at day 29 (week 4) using an NI margin of 10%.

Based on the ICH E10 and FDA NI guidance, the hypotheses for evaluating NI are as follows:

- Null hypothesis: the difference in percent reduction from baseline of total IgG at day 29 for the SC treatment arm compared with the IV treatment arm will be ≥10 (ie, μIV − μSC ≥10)
- Alternate hypothesis: the difference in percent reduction from baseline of total IgG at day 29 for the SC treatment arm compared with the IV treatment arm will be <10 (ie, μIV − μSC <10)

In ARGX-113-1704, the mean (SE) of total IgG percent reduction at week 4 of C1 was 62.2 (0.82) in the efgartigimod IV group and 0.1 (2.23) in the placebo group, which translates to a treatment effect of 62.1 with a 2-sided 95% CI of (57.44-66.76). With a NI margin of 10% in total IgG percent reduction, 84% (1–10/62.2×100%) of the PD effect is expected to be preserved.

Other objectives and endpoints

The secondary and exploratory endpoints were summarized with descriptive statistics by treatment arm and overall among all participants.

Similar to the primary analysis, a random-intercept model for the MG-ADL score with the percentage total IgG reduction from baseline as a predictor suggested that a decrease of 10% would translate into a preservation of 86% of the effect in reduction in MG-ADL change at week 4 (100×[1–0.35/2.5]). Week 4 was chosen as the time point to evaluate reduction in total IgG because it demonstrated the maximum reduction in total IgG 1 week after the last dose in C1. Several other measures of the PD effect on total IgG reduction, such as AUEC and Emax, were performed to support the justification of the NI margin for ARGX-113-2001.

Additional assessments of the association of PD parameters with clinical efficacy have been performed. For this assessment, the primary endpoint (MG-ADL responder) of ARGX-113-1704 was used. This endpoint is considered a representative endpoint because it concurs with the definition of a "consistent, maintained, and clinically relevant benefit." Most of the responders (84%) in ARGX-113-1704 were observed between week 1 and week 6.

To assess the impact of maximum total IgG reduction while accounting for the total IgG trajectory over weeks 1 to 4 of a cycle, the AUEC of percent reduction in total IgG was also evaluated in determining its relationship with MG-ADL response. Furthermore, the AUEC of percent reduction in total IgG is more representative for the overall exposure of the treatment captured by the PD marker, as opposed to a percent reduction in total IgG at a single time point (eg, week 4).

Based on data from C1 to C3 of ARGX-113-1704, the association between the average AUEC of percent total IgG reduction on the MG-ADL response was shown to be highly significant in the AChR-Ab seropositive population. The model predicted a loss of 3% to 4% clinical efficacy in terms of MG-ADL response, with a 10% less decrease in the average AUEC of percent IgG reduction between the baseline to week 4. Table below summarizes the predicted probability of MG-ADL response in AChR-Ab seropositive population.

Table 14: Study ARGX-113-1704: predicted probability of MG-ADL response at the average AUEC of percent reduction in total IgG with a 10% NI margin

	AChR-Ab seropositive population		Overall population	
Cycles 1 to 3 average value: baseline to week 4	**AUEC of percent reduction in total IgG**	**Probability of response**	**AUEC of percent reduction in total IgG**	**Probability of response**
Placebo group	–9.6	29.3 (21.2-38.8)	–10.3	37.6 (29.2-46.8)
Efgartigimod IV group	1183.9	69.9 (59.4-78.8)	1206.5	70.4 (61.6-77.9)
10% less decrease in the average AUEC of percent reduction of total IgG in the efgartigimod IV group	1064.5	66.2 (56.3-74.9)	1084.8	67.6 (59.1-74.9)

Source: Table 6
AChR-Ab=anti-acetylcholine receptor antibody; AUEC=area under the effect curve; GEE=generalized estimating equations; IgG=immunoglobulin gamma; IV=intravenous(ly); MG-ADL=Myasthenia Gravis Activities of Daily Living; NI=noninferiority
Note: The GEE with logit transformation was applied to model the MG-ADL binary outcome, and compound symmetry variance-covariance structure as a working correlation matrix was used to account for the nesting of cycles within participants.

Additionally, estimates of the PTE in terms of the MG-ADL response rates explained by AUEC of percent reduction in total IgG reduction (PD bridging marker) are high, indicating that a large part of the treatment effect (efgartigimod versus placebo) is mediated through the reduction in total IgG in ARGX-113-1704.

In a post-hoc manner, similar to the ANCOVA analysis of the primary endpoint, the percent change from baseline in AChR-Ab levels at day 29 was analysed using an ANCOVA model with treatment as a factor and baseline AChR-Ab levels as a covariate in AChR-Ab seropositive participants in the mITT analysis set. The p-value for testing the same null hypothesis of NI as specified in the protocol is provided.

- **Sample size**

Approximately 110 participants were planned to be enrolled and randomized in a 1:1 ratio to receive either efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg once weekly for 4 administrations in an open-label design.

The sample size was based on data from ARGX-113-1704 in participants with gMG (efgartigimod IV formulation) and ARGX-113-1907 in healthy participants (efgartigimod IV and SC formulations). The mean percent reduction in total IgG levels with the IV formulation was expected to be approximately 62 (SD: 7.5). Assuming a total IgG percent reduction from baseline at day 29 with efgartigimod PH20 SC of 60±7.5, 20 participants per treatment arm were needed for 90% power to detect NI at the 10% level using a 1-sided, 2-sample t-test at a 2.5% significance level. To account for attrition, 46 participants were planned to be recruited. The sample size was to be adjusted based on the SD of the total IgG percent reduction from baseline at day 29 in the SC arm of ARGX-113-1907. If the SD was 8.5 or 10, than the sample size was to be increased to 50 or 68, respectively. To account for attrition, additional participants per treatment arm (6 or 8, respectively) were to be added.

However, in protocol version 2.0 (Appendix 16.1.1) the sample size was increased to approximately 110 participants to provide better quantification of the clinical safety and efficacy profile of the PH20 SC formulation, and the IV formulation served as a reference treatment arm in this randomized study.

- **Randomisation and Blinding (masking)**

Randomization was stratified by Japanese versus non-Japanese participants. Within non-Japanese participants, randomization was further stratified by AChR-Ab status. Up to 20% of the randomized participants were expected to be seronegative for AChR-Ab in both the overall population and the Japanese participant population.

- **Statistical methods**

Clinical efficacy analyses were performed on the ITT analysis set. PD analyses were performed on the mITT analysis set. General characteristics, safety, and immunogenicity analyses were performed on the safety analysis set. The PK analysis set was used for the PK analysis. The AChR-Ab seropositive subset population was defined based on the actual laboratory results. All AEs and clinical laboratory abnormalities were treatment-emergent.

• ITT analysis set: all randomized participants who were exposed to the IMP

• mITT analysis set: all randomized participants with a value for total IgG levels at baseline and at least 1 postbaseline time point

• Safety analysis set: all randomized participants who were exposed to IMP

• PK analysis set: a subset of the safety analysis set with at least 1 postdose PK measurement

The primary endpoint was analysed using an ANCOVA model with treatment as a factor and total IgG levels at baseline as a covariate. The NI evaluation was based on a percent reduction from baseline in total IgG levels at day 29 (week 4) using an NI margin of 10%.

The secondary endpoints were summarized with descriptive statistics by treatment arm and overall among all participants. In addition, the difference in the percentage of MG-ADL responders between the 2 treatment arms was analysed using the meta-analysis predictive approach while incorporating treatment cycle 1 data from the efgartigimod IV treatment arm in ARGX-113-1704 as historically active controls (Bayesian hierarchical model).

The exploratory endpoints were summarized with descriptive statistics.

The planned analyses and determination of sample size are described in the final version of the SAP in Appendix 16.1.9, and provided in protocol version 2.0 in Appendix 16.1.1.

The following post hoc analyses were performed:

• After evaluating the MG-related procedures reported in the final locked study database, "enteral nutrition" was added as an MG-related procedure for statistical analysis.

• All prior therapies for myasthenia gravis that started before the first IMP administration, regardless of when they were stopped, were summarized.

• The ANCOVA analysis of the primary endpoint in the mITT analysis set, the per-protocol analysis set, and all AChR-Ab seropositive participants in the mITT analysis set was repeated to provide a p-value for testing the null hypothesis of NI as prespecified in the protocol. The SAP planned to provide the 2-sided 95% CI of the difference in the percentage of the total IgG reduction at week 4 between efgartigimod PH20 SC and

efgartigimod IV to evaluate NI by confirming whether the upper limit exceeded 10%. This is operationally equivalent to performing a 1-sided test at the 2.5% level using the prespecified ANCOVA model. A listing of participants who were not included in the ANCOVA analysis for the primary endpoint in the mITT analysis set was provided. A sensitivity analysis for the ANCOVA analysis of the primary endpoint in the mITT analysis set was performed by imputing missing primary endpoint data with the first value at or after the last IMP administration.

• Similar to the ANCOVA analysis of the primary endpoint, the percent change from baseline in AChR-Ab levels at day 29 was analysed using an ANCOVA model with treatment as a factor and baseline AChR-Ab levels as a covariate in AChR-Ab seropositive participants in the mITT analysis set. The p-value for testing the same null hypothesis of NI as specified in the protocol is provided.

• A sensitivity analysis of the actual values and percent change from baseline in total IgG levels and IgG subtypes over time was performed by excluding results for all IgG assessments after administration of IVIg or plasmapheresis rescue therapy.

• Additional analyses on the reported QMG total score were performed, including descriptive statistics of the actual values and changes from baseline by AChR-Ab status and frequency tabulations of actual values and changes from baseline for the overall population and by AChR-Ab status.

• Injection site reactions, defined by the Medical Dictionary for Regulatory Activities (MedDRA) high-level term of Injection site reactions, were summarized by System Organ Class (SOC) and preferred term (PT). In the efgartigimod PH20 SC arm, data were further summarized by outcome and toxicity grade. The prevalence and incidence of Injection site reactions by injection period and the number and percentage of participants who had Injection site reactions by number of injections in participants with 4 administrations were also summarized.

• A correlation analysis between immunogenicity and Injection site reactions was performed.

Results

- **Participant flow**

Of the 153 participants screened for inclusion, 34 (22.2%) participants did not meet the eligibility criteria.

A total of 111 participants were enrolled and randomized: 55 participants in the efgartigimod PH20 SC arm and 56 in the efgartigimod IV arm. One participant was randomized to the efgartigimod IV arm but did not receive efgartigimod due to an AE.

Table 15: Participant disposition (safety analysis set)

	EFG PH20 SC (N=55) n (%)	EFG IV (N=55) n (%)	Total (N=110) n (%)
Overall Treatment	**55 (100)**	**55 (100)**	**110 (100)**
Completed	52 (94.5)	55 (100)	107 (97.3)
Discontinued	3 (5.5)	0	3 (2.7)
Primary reason for treatment discontinuation			
Adverse event	2 (3.6)	0	2 (1.8)
Other	1 (1.8)	0	1 (0.9)
Overall Study	**55 (100)**	**55 (100)**	**110 (100)**
Completed	54 (98.2)	54 (98.2)	108 (98.2)
Discontinued	1 (1.8)	1 (1.8)	2 (1.8)
Primary reason for study discontinuation			
Other	1 (1.8)	0	1 (0.9)
Withdrawal by participant	0	1 (1.8)	1 (0.9)

A total of 53 (96.4%) participants in the efgartigimod PH20 SC arm and 52 (94.5%) participants in the efgartigimod IV arm rolled over to ARGX-113-2002.

In the efgartigimod PH20 SC arm, 49 (89.1%) participants received all 4 doses. In the efgartigimod IV arm, 55 (100%) participants received all 4 doses. Two (3.6%) participants discontinued treatment due to AEs and missed 3 doses. One participant missed the third dose as the result of a treatment interruption due to an AE/SAE. Additionally, 1 participant missed the third dose due to a missed study visit, and 1 participant missed the second dose due to an unknown reason. Per protocol, participants who missed a dose were not required to be discontinued from IMP and could continue in the study.

- **Recruitment**

Study Initiation Date: 05 Feb 2021 (first participant's first visit)

Study Completion Date: 13 Dec 2021 (last participant's last visit)

This study was conducted at 43 sites that randomized participants in Belgium, Georgia, Germany, Hungary, Italy, Japan, Netherlands, Poland, Russia, Spain, and the United States.

- **Conduct of the study**

The original protocol, version 1.0 (15 Oct 2020), was amended once (version 2.0, 02 Jul 2021). In addition, data were analysed according to the SAP version 1.0, dated 01 Feb 2022. An independent Data Safety Monitoring Board (DSMB) periodically reviewed and evaluated the accumulated study data for participant safety, study conduct, and study progress. Major protocol deviations led to the exclusion of 6 (10.9%) participants in each arm from the per-protocol analysis set.

- **Baseline data**

Table 16: Participant Demographics (Safety Analysis Set)

	EFG PH20 SC (N=55)	EFG IV (N=55)	Total (N=110)
Age (years)			
n	55	55	110
Mean (SD)	50.9 (15.78)	55.8 (15.35)	53.4 (15.69)
Median (min, max)	53.0 (19, 84)	59.0 (24, 83)	53.5 (19, 84)
Age category, n (%)			
18 - <65 years	43 (78.2)	37 (67.3)	80 (72.7)
≥65 years	12 (21.8)	18 (32.7)	30 (27.3)
Sex, n (%)			
Female	31 (56.4)	34 (61.8)	65 (59.1)
Male	24 (43.6)	21 (38.2)	45 (40.9)
Race, n (%)			
Asian	4 (7.3)	4 (7.3)	8 (7.3)
Japanese	4 (7.3)	4 (7.3)	8 (7.3)
Multiple	1 (1.8)	0	1 (0.9)
White	50 (90.9)	51 (92.7)	101 (91.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (5.5)	2 (3.6)	5 (4.5)
Not Hispanic or Latino	52 (94.5)	53 (96.4)	105 (95.5)
Japanese participants as defined in the study protocol, n (%)			
No	51 (92.7)	51 (92.7)	102 (92.7)
Yes	4 (7.3)	4 (7.3)	8 (7.3)
Weight (kg)			
n	55	55	110
Mean (SD)	79.75 (21.115)	81.47 (22.167)	80.61 (21.565)
Median (min, max)	78.30 (42.0, 150.2)	78.00 (45.0, 139.3)	78.00 (42.0, 150.2)

Source: Table 14.1.2.1
EFG=efgartigimod; IV=intravenous(ly); max=maximum; min=minimum; n=number of participants for whom the observation was reported; N=number of participants per arm in the analysis set; SC=subcutaneous(ly)
Note: The denominator for the percentage calculations was the total number of participants per arm in the analysis set, excluding missing values.

Table 17: Study ARGX-113-2001 Participant Demography for AChR-Ab seropositive population (Safety Analysis set)

	EFG PH20 SC (N=45)	EFG IV (N=46)	Total (N=91)
Age at screening (years)			
n	45	46	91
Mean (SD)	51.3 (16.27)	57.0 (14.84)	54.1 (15.74)
Median (min, max)	53.0 (19, 84)	60.0 (24, 83)	57.0 (19, 84)
Age category, n (%)			
18 - <65 years	35 (77.8)	30 (65.2)	65 (71.4)
≥65 years	10 (22.2)	16 (34.8)	26 (28.6)
Sex, n (%)			
Female	25 (55.6)	26 (56.5)	51 (56.0)
Male	20 (44.4)	20 (43.5)	40 (44.0)
Race, n (%)			
Asian	3 (6.7)	3 (6.5)	6 (6.6)
Japanese	3 (6.7)	3 (6.5)	6 (6.6)
Multiple	1 (2.2)	0	1 (1.1)
White	41 (91.1)	43 (93.5)	84 (92.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (6.7)	1 (2.2)	4 (4.4)
Not Hispanic or Latino	42 (93.3)	45 (97.8)	87 (95.6)
Japanese participants as defined in the study protocol, n (%)			
No	42 (93.3)	43 (93.5)	85 (93.4)
Yes	3 (6.7)	3 (6.5)	6 (6.6)
Weight (kg)			
n	45	46	91
Mean (SD)	77.28 (19.566)	83.88 (22.825)	80.62 (21.417)
Median (min, max)	76.90 (42.0; 115.4)	81.65 (46.9; 139.3)	78.30 (42.0; 139.3)

Source: Module 5.3.5.1, ARGX-113-2001 EMA output, Table 14.1.2.1
AChR-Ab= anti-acetylcholine receptor antibody; EFG IV=efgartigimod formulation for IV administration; EFG PH20 SC=efgartigimod for SC administration coformulated with recombinant human hyaluronidase PH20; EMA=European Medicines Agency; IV=intravenous; max=maximum; min=minimum; N=number of participants per arm in the analysis set; n=number of participants for whom the observation was reported; SC=subcutaneous
Note: The denominator for the percentage calculations was the total number of participants per arm in the analysis set, excluding missing values.

Table 18: Baseline Disease Characteristics (Safety Analysis Set)

	EFG PH20 SC (N=55)	EFG IV (N=55)	Total (N=110)
Time since diagnosis (years)			
n	55	55	110
Mean (SD)	6.32 (6.413)	7.74 (8.478)	7.03 (7.516)
Median (min, max)	4.41 (0.5, 33.0)	4.60 (0.1, 40.4)	4.51 (0.1, 40.4)
Time since thymectomy (years)			
n	16	13	29
Mean (SD)	5.85 (4.057)	6.63 (6.214)	6.20 (5.052)
Median (min, max)	5.61 (0.8, 13.3)	5.75 (0.2, 24.2)	5.62 (0.2, 24.2)
MGFA classification at screening, n (%)			
Class II-IIa	13 (23.6)	11 (20.0)	24 (21.8)
Class II-IIb	16 (29.1)	11 (20.0)	27 (24.5)
Class III-IIIa	15 (27.3)	18 (32.7)	33 (30.0)
Class III-IIIb	9 (16.4)	12 (21.8)	21 (19.1)
Class IV-Iva	0	2 (3.6)	2 (1.8)
Class IV-IVb	2 (3.6)	1 (1.8)	3 (2.7)
MG-ADL total score at screening			
n	55	55	110
Mean (SD)	8.7 (2.46)	8.7 (2.62)	8.7 (2.53)
Median (min, max)	8.0 (5, 15)	8.0 (5, 15)	8.0 (5, 15)
MG-ADL total score at baseline			
N	55	55	110
Mean (SD)	8.8 (2.58)	8.5 (2.64)	8.7 (2.60)
Median (min, max)	8.0 (5, 16)	8.0 (5, 15)	8.0 (5, 16)
MG-ADL total score category at baseline, n (%)			
5-7	20 (36.4)	24 (43.6)	44 (40.0)
8-9	16 (29.1)	12 (21.8)	28 (25.5)
≥10	19 (34.5)	19 (34.5)	38 (34.5)
QMG total score at baseline			
n	55	55	110
Mean (SD)	14.9 (4.40)	15.5 (4.48)	15.2 (4.43)
Median (min, max)	15.0 (3, 25)	16.0 (7, 27)	15.0 (3, 27)
AChR-Ab status, n (%)			
Seronegative	10 (18.2)	9 (16.4)	19 (17.3)
Seropositive	45 (81.8)	46 (83.6)	91 (82.7)

Source: Table 14.1.2.2
AChR-Ab=anti-acetylcholine receptor antibody; EFG=efgartigimod; IV=intravenous(ly); max=maximum; min=minimum; N=number of participants per arm in the analysis set; n=number of participants for whom the observation was reported; SC=subcutaneous(ly)
Note: The denominator for the percentage calculations is the total number of participants per arm in the analysis set, excluding missing values.

Table 19: Study ARGX-113-2001 Baseline disease characteristics for the AChR-Ab seropositive participants (safety analysis set)

	EFG PH20 SC (N=45)	EFG IV (N=46)	Total (N=91)
Time since diagnosis (years)			
n	45	46	91
Mean (SD)	6.69 (6.743)	7.88 (8.950)	7.29 (7.914)
Median (min, max)	4.56 (0.6, 33.0)	4.03 (0.1, 40.4)	4.41 (0.1, 40.4)
Time since thymectomy (years)			
n	14	12	26
Mean (SD)	5.34 (3.803)	6.71 (6.484)	5.97 (5.148)
Median (min, max)	5.12 (0.8; 12.5)	5.29 (0.2; 24.2)	5.12 (0.2; 24.2)
MGFA classification at screening, n (%)			
Class II-IIa	9 (20.0)	7 (15.2)	16 (17.6)
Class II-IIb	16 (35.6)	10 (21.7)	26 (28.6)
Class III-IIIa	11 (24.4)	17 (37.0)	28 (30.8)
Class III-IIIb	8 (17.8)	10 (21.7)	18 (19.8)
Class IV-IVa	0	2 (4.3)	2 (2.2)
Class IV-IVb	1 (2.2)	0	1 (1.1)

	EFG PH20 SC (N=45)	EFG IV (N=46)	Total (N=91)
MG-ADL total score at screening			
n	45	46	91
Mean (SD)	8.4 (2.54)	8.3 (2.41)	8.4 (2.46)
Median (min, max)	8.0 (5; 15)	8.0 (5; 14)	8.0 (5; 15)
MG-ADL total score at baseline			
n	45	46	91
Mean (SD)	8.6 (2.62)	8.3 (2.51)	8.5 (2.56)
Median (min, max)	8.0 (5; 16)	8.0 (5; 15)	8.0 (5; 16)
MG-ADL total score category at baseline, n (%)			
5-7	19 (42.2)	21 (45.7)	40 (44.0)
8-9	12 (26.7)	11 (23.9)	23 (25.3)
≥10	14 (31.1)	14 (30.4)	28 (30.8)
QMG total score at baseline			
n	45	46	91
Mean (SD)	14.4 (4.42)	15.1 (4.28)	14.8 (4.34)
Median (min, max)	14.0 (3; 25)	15.0 (7; 25)	15.0 (3; 25)

Source: Module 5.3.5.1, ARGX-113-2001 EMA output, Table 14.1.2.2
AChR-Ab=anti-acetylcholine receptor antibody; EFG IV=efgartigimod formulation for IV administration; EFG PH20 SC=efgartigimod for SC administration coformulated with recombinant human hyaluronidase PH20; EMA=European Medicines Agency; IV=intravenous; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGFA=Myasthenia Gravis Foundation of America; max=maximum; min=minimum; N=number of participants per arm in the analysis set; n=number of participants for whom the observation was reported; QMG=Quantitative Myasthenia Gravis; SC=subcutaneous
Note: The denominator for the percentage calculations is the total number of participants per arm in the analysis set, excluding missing values.

Table 20: Baseline MG Therapies Used During the Study (Safety Analysis Set)

	EFG PH20 SC (N=55) n (%)	EFG IV (N=55) n (%)	Total (N=110) n (%)
≥1 Baseline MG therapy[a]	55 (100)	54 (98.2)	109 (99.1)
≥2 Baseline MG therapies[a]	38 (69.1)	38 (69.1)	76 (69.1)
≥3 Baseline MG therapies[a]	19 (34.5)	14 (25.5)	33 (30.0)
Any steroid	40 (72.7)	33 (60.0)	73 (66.4)
Deflazacort	0	3 (5.5)	3 (2.7)
Methylprednisolone	10 (18.2)	6 (10.9)	16 (14.5)
Prednisolone	10 (18.2)	10 (18.2)	20 (18.2)
Prednisolone acetate	0	1 (1.8)	1 (0.9)
Prednisone	20 (36.4)	13 (23.6)	33 (30.0)
Any NSID	23 (41.8)	25 (45.5)	48 (43.6)
Azathioprine	12 (21.8)	8 (14.5)	20 (18.2)
Ciclosporin	2 (3.6)	6 (10.9)	8 (7.3)
Methotrexate	3 (5.5)	3 (5.5)	6 (5.5)
Mycophenolate mofetil	3 (5.5)	7 (12.7)	10 (9.1)
Tacrolimus	3 (5.5)	0	3 (2.7)
Tacrolimus monohydrate	0	1 (1.8)	1 (0.9)
Any AChE inhibitor	48 (87.3)	47 (85.5)	95 (86.4)
Ambenonium chloride	4 (7.3)	3 (5.5)	7 (6.4)
Distigmine bromide	1 (1.8)	0	1 (0.9)
Pyridostigmine	11 (20.0)	13 (23.6)	24 (21.8)
Pyridostigmine bromide	35 (63.6)	32 (58.2)	67 (60.9)
Single therapy	17 (30.9)	16 (29.1)	33 (30.0)
Steroids	5 (9.1)	4 (7.3)	9 (8.2)
NSIDs	1 (1.8)	0	1 (0.9)
AChE inhibitors	11 (20.0)	12 (21.8)	23 (20.9)
Double therapy	20 (36.4)	25 (45.5)	45 (40.9)
Steroids + NSIDs	1 (1.8)	3 (5.5)	4 (3.6)
Steroids + AChE inhibitors	16 (29.1)	13 (23.6)	29 (26.4)
NSIDs + AChE inhibitors	3 (5.5)	9 (16.4)	12 (10.9)
Triple therapy	18 (32.7)	13 (23.6)	31 (28.2)
Steroids + NSIDs + AChE inhibitors	18 (32.7)	13 (23.6)	31 (28.2)

Source: Tables 14.1.2.8 and 14.1.2.9
AChE=acetylcholinesterase; AChR-Ab=anti-acetylcholine receptor antibody; EFG=efgartigimod; IMP=investigational medicinal product; IV=intravenous(ly); MG=myasthenia gravis; N=number of participants per arm in the analysis set; n=number of participants for whom the observation was reported; NSID=nonsteroidal immunosuppressive drug; SC=subcutaneous(ly)
Note: Baseline MG therapies were defined as prior MG therapies that were ongoing after the first IMP administration.
[a] The number of baseline MG therapies may include more than 1 class of medication (ie, steroids + NSIDs + AChE inhibitors).

- **Numbers analysed**

A total of 111 participants were enrolled and randomized to receive the investigational medicinal product (IMP): 55 participants in the efgartigimod PH20 SC arm and 56 participants in the efgartigimod IV arm. There were 110 participants (55 in each arm) in the safety analysis set and the ITT and mITT analysis sets.

- **Outcomes and estimation**

Primary Endpoint

The primary PD endpoint was the percent reduction from baseline in total IgG levels at day 29. Total IgG reduction at day 29 in participants with gMG who received efgartigimod PH20 SC 1000 mg was NI to that in participants who received efgartigimod IV 10 mg/kg after 1 treatment cycle of 4 weekly administrations (refer to the PD results section above).

Table 21: ANCOVA analysis of percent change from baseline in total IgG level at day 29 (mITT analysis set)

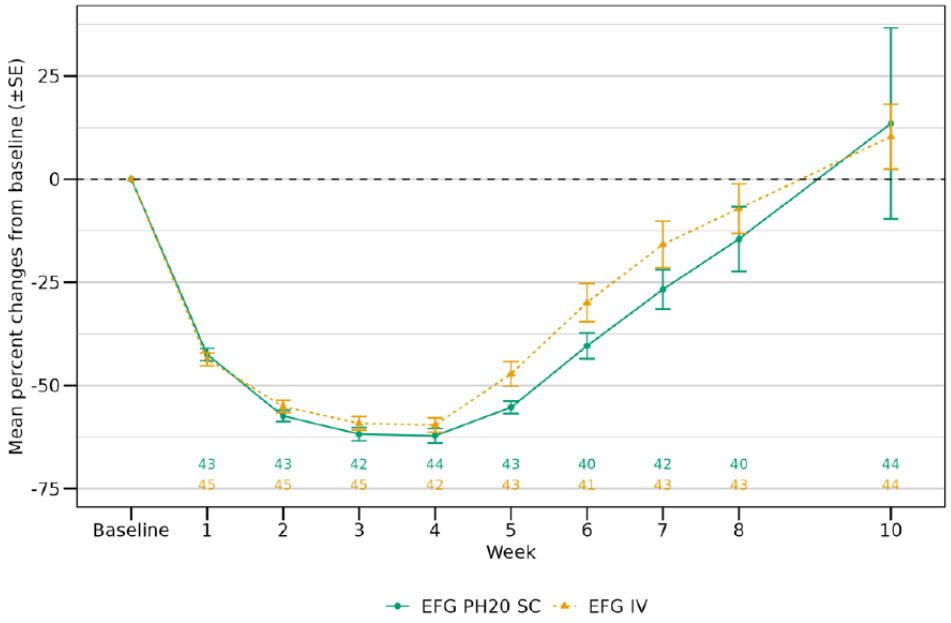
Efgartigimod alfa SC			**Efgartigimod alfa IV**			**Efgartigimod alfa SC versus efgartigimod alfa IV**		
N	**LS Mean**	**95% CI**	**N**	**LS Mean**	**95% CI**	**LS of Mean difference**	**95% CI**	**p-value**
AChR-Ab seropositive								
41	-66.9	-69.78, -64.02	43	-62.4	-65.22, -59.59	-4.5	-8.53, -0.46	<0.0001

AChR-Ab=acetylcholine receptor–antibody; ANCOVA=analysis of covariance; CI = confidence interval; SC: subcutaneous; IV: intravenous; LS=least squares; mITT=modified intent-to-treatment analysis set; N= number of patients per group that were included in the ANCOVA analysis

Post hoc Analysis - Reduction in AChR-Ab levels

Decreases in AChR-Ab levels followed a comparable time course as total IgG levels in AChR-Ab positive patients and were similar between the efgartigimod alfa SC and IV groups. Maximum mean percentage decreases in AChR-Ab levels of 62.2% and 59.6% were observed one week after the last administration in the efgartigimod alfa SC and IV groups, respectively (figure below).

Figure 31: AChR-Ab Levels Percent Change From Baseline Over Time (mITT Analysis Set)



Secondary Efficacy Endpoints

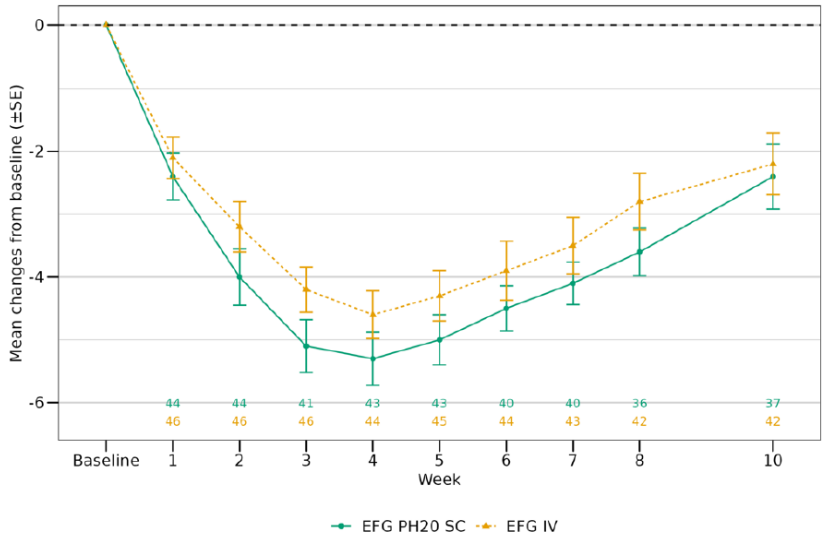
The clinical efficacy of efgartigimod PH20 SC, using validated clinical outcome scales including the participant-reported MG-ADL scale and the physician-assessed QMG scale, was similar to the clinical efficacy of efgartigimod IV after 1 treatment cycle of 4 weekly administrations (table and figures below).

Table 22: MG-ADL and QMG responders at day 29 (mITT analysis set)

	Population	Efgartigimod alfa SC n/N (%)	Efgartigimod alfa IV n/N (%)	Difference Efgartigimod alfa SC-Efgartigimod alfa IV (95% CI)
MG-ADL	AChR-Ab seropositive	32/45 (71.1)	33/46 (71.7)	−0.6 (−19.2 to 17.9)
QMG	AChR-Ab seropositive	31/45 (68.9)	24/45 (53.3)	15.6 (−4.3 to 35.4)

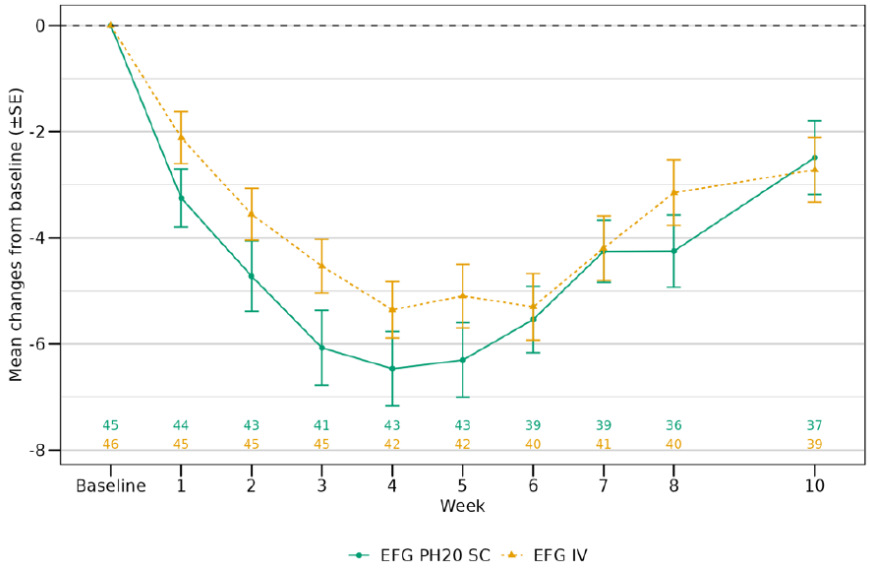
AChR-Ab = acetylcholine receptor-antibody; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; SC = subcutaneous; IV = intravenous; mITT = modified intent-to-treat; n = number of patients for whom the observation was reported; N = number of patients in the analysis set; CI = confidence interval.

Figure 32: MG-ADL Total Score Change From Baseline Over Time for the AChR-Ab Seropositive Population (ITT Analysis Set)



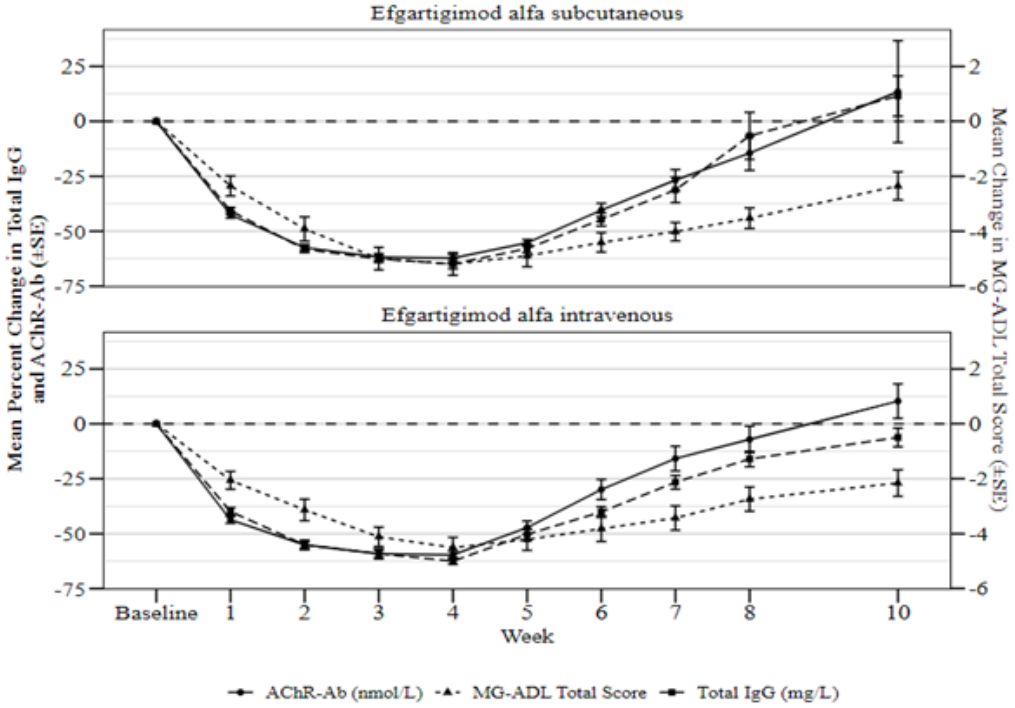
Source: Table 14.2.3.2.2
AChR-Ab=anti-acetylcholine receptor antibody; EFG=efgartigimod; ITT=intent-to-treat; IV=intravenous(ly); MG-ADL=Myasthenia Gravis Activities of Daily Living; SC=subcutaneous(ly)

Figure 33: QMG Total Score Change From Baseline Over Time for the AChR-Ab Seropositive Population (ITT Analysis Set)



Relationship of PD and Clinical endpoints

Figure 34: Relationship between change in levels of total IgG and AChR- Ab and change in MG ADL total score in AChR-Ab seropositive population (study ARGX-113-2001)



- **Ancillary analyses**

In ARGX-113-2001 and ARGX-113-2002, 168 participants received efgartigimod PH20 SC. Of these 168 participants, 36 were aged ≥65 years, with 28 participants aged 65 to 74 years, and 8 participants aged 75 to 84 years. No participants were aged >85 years.

A summary of the number of participants aged ≥65 years in ARGX-113-2001 and ARGX-113-2002 is provided by age category below.

	Age categories ≥65 years		
	Age 65-74 (older participants number / total number)	**Age 75-84 (older participants number / total number)**	**Age 85+ (older participants number / total number)**
ARGX-113-2001	10/55	2/55	0/55
ARGX-113-2002[a]	18/113	6/113	0/113
Overall	**28/168**	**8/168**	**0/168**

Source: Module 5.3.5.1, ARGX-113-2001 CSR, Listing 16.2.4.1; Module 5.3.5.2, ARGX-113-2002-IA1 CSR, Listing 16.2.4.1

Note: Number of participants receiving at least 1 dose of efgartigimod PH20 SC.

[a] Number of participants who did not receive efgartigimod PH20 SC in the antecedent ARGX-113-2001.

- **Summary of main efficacy results**

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 23: Summary of efficacy for trial ARGX-113-2001

Title: A Phase 3, Randomized, Open-label, Parallel-Group Study to Compare the Pharmacodynamics, Pharmacokinetics, Efficacy, Safety, Tolerability, and Immunogenicity of Multiple Subcutaneous Injections of Efgartigimod PH20 SC With Multiple Intravenous Infusions of Efgartigimod in Patients With Generalized Myasthenia Gravis			
Study identifier	Study Number: ARGX-113-2001 EudraCT: 2020-004085-19 NCT: NCT04735432		
Design	Phase 3, multicenter, randomized, open-label, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	10 weeks (3-week treatment period and a 7-week follow-up period) 2 weeks (screening period) not applicable	
Hypothesis	Non-inferiority		
Treatments groups	efgartigimod alfa subcutaneous (EFG PH20 SC)	efgartigimod PH20 SC 1000 mg, one treatment cycle of once weekly injections for 4 weeks (N=55)	
	efgartigimod alfa intravenous (EFG IV)	efgartigimod IV 10 mg/kg, , one treatment cycle of once weekly injections for 4 weeks (N=56)	
Endpoints and definitions	Primary endpoint	Percent reduction from baseline in total IgG levels at day 29 (ie, 7 days after the fourth IV or SC administration)	
	Posthoc analysis	Percent change from baseline in anti-AChR antibodies at week 4	
	Secondary endpoint	Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders, defined as participants with a reduction of ≥2 points from baseline on the MG-ADL score for ≥4 consecutive weeks occurring at latest 1 weeks after last IMP administration	
	Secondary endpoint	Number and percentage of Quantitative Myasthenia Gravis (QMG) responders, defined as participants with a reduction of ≥3 points from baseline on the QMG score for ≥4 consecutive weeks occurring at the latest 1 week after last administration of IMP	
	Secondary endpoint	Change from baseline in MG-ADL total score over time	
	Secondary endpoint	Change from baseline in QMG score over time	
Database lock	04 February 2022		
Results and Analysis			

Analysis description	**Primary Analysis:** Percent reduction from baseline in total IgG levels at day 29 (ie, 7 days after the fourth IV or SC administration)			
Analysis population and time point description	Overall population in modified intent-to-treatment analysis set At day 29			
Descriptive statistics and estimate variability	Treatment group	**EFG PH20 SC**	**EFG IV**	**EFG PH20 SC vs EFG IV**
	Number of subject	50	52	
	Least-squares	-66.4	-62.2	-4.2
	95% CI	-68.91 to -63.86	-64.67 to -59.72	-7.73 to -0.66
	p-value			<0.0001
Analysis population and time point description	AChR-Ab seropositive participants in modified intent-to-treatment analysis set At day 29			
Descriptive statistics and estimate variability	Treatment group	**EFG PH20 SC**	**EFG IV**	**EFG PH20 SC vs EFG IV**
	Number of subject	41	43	
	Least-squares	-66.9	-62.4	-4.5
	95% CI	−69.78 to −64.02	- 65.22 to −59.59	- 8.53 to −0.46
	p-value			<0.0001
Analysis description	***Post hoc* Analysis:** Percent change from baseline in anti-AChR antibodies at week 4 (ie, 7 days after the fourth IV or SC administration)			
Analysis population and time point description	AChR-Ab seropositive participants in modified intent-to-treatment analysis set At day 29. ANCOVA model with treatment as factor and baseline AChR-Ab (in nmol/L) as covariate.			
Descriptive statistics and estimate variability	Treatment group	**EFG PH20 SC**	**EFG IV**	**EFG PH20 SC vs EFG IV**
	Number of subject	44	42	
	Least-squares	-62.2	-59.7	-2.5
	95% CI	-65.64 to -58.75	-63.19 to -56.15	-7.45 to 2.41
	p-value			<0.0001

Analysis description	**Secondary analysis:** Number and percentage of Myasthenia Gravis Activities of Daily Living (MG-ADL) responders			
Analysis population and time point description	Overall population and AChR-Ab seropositive participants in intent-to-treatment analysis set			
Secondary key endpoint 1 Descriptive statistics and estimate variability	Responders	**EFG PH20 SC** **n/N (%)**	**EFG IV** **n/N (%)**	**Difference in response (95% CI)**
	Overall population	38/55 (69.1)	38/55 (69.1)	0.0 (−17.3 to 17.3)
	AChR-Ab seropositive	32/45 (71.1)	33/46 (71.7)	-0.6 (-19.2 to 17.9)
Analysis description	**Secondary analysis:** Number and percentage of Quantitative Myasthenia Gravis (QMG) responders			
Analysis population and time point description	Overall population and AChR-Ab seropositive participants in modified intent-to-treatment analysis set			
Secondary key endpoint 2 Descriptive statistics and estimate variability	Responder	**EFG PH20 SC** **n/N (%)**	**EFG IV** **n/N (%)**	**Difference in response (95% CI)**
	Overall population	36/55 (65.5)	28/54 (51.9)	13.6 (−4.7 to 31.9)
	AChR-Ab seropositive	31/45 (68.9)	24/45 (53.3)	15.6 (-4.3 to 35.4)
Analysis description	**Secondary analysis:** Change from baseline in MG-ADL total score over time			
Analysis population and time point description	Overall population and AChR-Ab seropositive participants in intent-to-treatment analysis set At week 4 and at week 10			

Secondary key endpoint 3 Descriptive statistics and estimate variability		**EFG PH20 SC**		**EFG IV**		**EFG PH20 SC vs EFG IV**	
	Visit	n	Mean (SE)	n	Mean (SE)	Mean	95% CI
	Overall population						
	Week 4	52	−5.1 (0.38)	53	−4.7 (0.37)	−0.4	−1.46 to 0.62
	Week 10	46	−2.2 (0.44)	51	−2.1 (0.43)	−0.1	−1.35 to 1.11
	AChR-Ab seropositive population						
	Week 4	43	-5.3 (0.42)	44	-4.6 (0.38)	-0.7	-1.83 to 0.41
	Week 10	37	−2.4 (0.52)	42	−2.2 (0.49)	-0.2	−1.62 to 1.23

Analysis description	**Secondary analysis:** Change from baseline in QMG score over time						
Analysis population and time point description	Overall population and AChR-Ab seropositive participants in intent-to-treatment analysis set At week 4 and week 10						
Secondary key endpoint 4 Descriptive statistics and estimate variability		**EFG PH20 SC**		**EFG IV**		**EFG PH20 SC vs EFG IV**	
	Visit	n	Mean (SE)	n	Mean (SE)	Mean	95% CI
	Overall population						
	Week 4	52	−6.1 (0.62)	51	−5.2 (0.52)	-0.9	−2.46 to 0.74
	Week 10	46	−2.3 (0.60)	48	−2.8 (0.53)	0.5	−1.10 to 2.07
	AChR-Ab seropositive population						
	Week 4	43	-6.5 (0.70)	42	-5.4 (0.53)	-1.1	-2.86 to 0.64
	Week 10	37	−2.5 (0.70)	39	−2.7 (0.61)	0.2	−1.61 to 2.07

2.5.5.3. Supportive study(ies)

Table 24: Overview of Attributes in the Phase 3 Clinical Studies Supporting Efficacy of Efgartigimod PH20 SC and Efgartigimod IV in Participants With gMG

	ARGX-113-2001 Efgartigimod PH20 SC or efgartigimod IV	**ARGX-113-1704 Efgartigimod IV or placebo**	**ARGX-113-2002 Efgartigimod PH20 SC**	**ARGX-113-1705 Efgartigimod IV**
Status	Completed Last participant completed: 13 Dec 2021	Completed Last participant completed: 06 Apr 2020	Ongoing IA1 data cutoff: 02 Mar 2022 (12 Jan 2022 for bioanalytical data)	Ongoing IA4 Data cutoff: 31 Jan 2022 (09 Dec 2021 for bioanalytical data)
Design	Open-label, randomized, parallel-group	Randomized, double-blinded, placebo-controlled	Open-label extension of ARGX-113-2001 and ARGX-113-1705	Open-label extension of ARGX-113-1704
Study duration	12 weeks	up to 28 weeks	2 years	Part A: 1 year Part B: ≤2 years
IMP dosage and administration	efgartigimod IV 10 mg/kg once weekly for a total of 4 infusions or efgartigimod PH20 SC 1000 mg once weekly for a total of 4 injections	• efgartigimod IV 10 mg/kg or placebo • IV infusions in treatment cycles of 4 infusions at weekly intervals (once weekly for 4 infusions) • retreatment/subsequent cycles of 4 infusions at weekly intervals based on clinical evaluation by investigator[a]	• efgartigimod PH20 SC 1000 mg • SC injections in treatment cycles of 4 injections at weekly intervals (once weekly) • retreatment/subsequent cycles of 4 injections at weekly intervals based on clinical evaluation by investigator[b] • administered in 3-week treatment periods, repeated as needed with at least 28 days in between treatment periods	• efgartigimod IV 10 mg/kg • IV infusions in treatment cycles of 4 infusions at weekly intervals • retreatment/subsequent cycles of 4 infusions at weekly intervals based on clinical evaluation by investigator[c,d]
Participants analyzed	• efgartigimod PH20 SC: N=55 • efgartigimod IV: N=55	• efgartigimod IV: N=84 • placebo IV: N=83	• total: N=164[e] • prior SC 2001: N=51[f] • prior IV 2001: N=48[g] • prior IV 1705: N=65[h] • total IV (1705+2001): N=113[i]	• efgartigimod-efgartigimod: N=77[j] • placebo-efgartigimod: N=68[k] • total efgartigimod: N=145[l]
Maximum # of treatment cycles	1 cycle	3 cycles	Maximum of 14 treatment cycles[b]	• Approximately 7 in Part A[c] • Cycles as required in opinion of treating physician in Part B[d]
Study population				
Baseline MG-ADL score	≥5	≥5	NA	NA
Baseline AChR-Ab status[m]	AChR-Ab seropositive/seronegative[m]	AChR-Ab seropositive/seronegative[m]	AChR-Ab seropositive/seronegative	AChR-Ab seropositive/seronegative
Primary objective	To demonstrate that the PD effect of 4 weekly injections of efgartigimod PH20 SC 1000 mg is NI by an NI margin of 10% to that of 4 weekly infusions of efgartigimod IV 10 mg/kg	To evaluate the efficacy of efgartigimod IV in the AChR-Ab seropositive population as assessed by the percentage of MG-ADL responders during C1[n]	To evaluate the long-term safety and tolerability of efgartigimod PH20 SC in participants with gMG	To evaluate the long-term safety and tolerability of efgartigimod IV in AChR-Ab seropositive participants

	ARGX-113-2001 Efgartigimod PH20 SC or efgartigimod IV	ARGX-113-1704 Efgartigimod IV or placebo	ARGX-113-2002 Efgartigimod PH20 SC	ARGX-113-1705 Efgartigimod IV
Study endpoints				
Primary endpoint	NI of the PD effect of efgartigimod PH20 SC compared to efgartigimod IV	MG-ADL responders in the AChR-Ab seropositive population[n]	Long-term safety and tolerability of efgartigimod PH20 SC	Long-term safety and tolerability of efgartigimod IV in AChR-Ab seropositive population
Efficacy assessments	• Proportion of participants who were MG-ADL responders • Proportion of participants who were QMG responders • Change in MG-ADL total score • Change in QMG total score	• Proportion of participants who were MG-ADL responders in AChR-Ab seropositive and overall population • Proportion of participants who were QMG responders • Change in MG-ADL total score • Change in QMG total score • Change in MGC • % time patients have CMI in MG-ADL • Time to qualification for retreatment • Duration of response in MG-ADL responders	Change in MG-ADL total score	• Change in MG-ADL total score • Change in QMG total score (Part A only) • % of patients with ≥2-or ≥3- point reduction in MG-ADL total score
Quality of life endpoints	NA	• EQ-5D-5L • MG-QoL15r	• EQ-5D-5L • MG-QoL15r	NA
Pharmacodynamic endpoints	• Change in total IgG, IgG subtypes, and AChR-Ab • AUEC of the percent reduction from baseline in total IgG, AChR-Ab and IgG subtypes[o]	Change in total IgG, IgG subtypes, AChR-Ab, and anti-MuSK antibodies	Change in total IgG and AChR-Ab	Part A only: Change in total IgG, IgG subtypes, AChR-Ab, and anti-MuSK antibodies

AChR-Ab=anti-acetylcholine receptor antibody; AUEC=area under the effect curve; C1=cycle 1; CMI=clinically meaningful improvement; efgartigimod IV=efgartigimod formulation for IV administration; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; gMG=generalized myasthenia gravis; IA=interim analysis; IgG=immunoglobulin gamma; IMP=investigational medicinal product; IV=intravenous(ly); MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; MG-QoL15r=15-Item Quality of Life Scale for Myasthenia Gravis (revised version); MuSK=muscle-specific kinase; N=number of participants; NA=not applicable; NI=noninferior/ity; PD=pharmacodynamic; QMG=Quantitative Myasthenia Gravis; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Note: A cycle is defined as the period including the treatment period (4 weekly administrations) and the corresponding intertreatment period ending immediately before the first dose of the next treatment period. A treatment period and its corresponding intertreatment period were grouped into cycles for analysis.
An intertreatment period is defined as the time between the last efgartigimod administration of the treatment period and the first efgartigimod administration of the subsequent treatment period.

[a] In ARGX-113-1704, participants could receive a new cycle with efgartigimod, if the following criteria were met: (1) An MG-ADL total score ≥5 points with more than 50% of the total score due to nonocular symptoms, and (2) A participant who no longer shows a decrease of ≥2 points on the total MG-ADL score compared to the corresponding treatment cycle baseline.

[b] In ARGX-113-2002, a participant may be retreated in another cycle if the investigator determines that the participant's condition has deteriorated due to gMG symptoms, and if the participant agrees to be retreated.

[c] In Part A of ARGX-113-1705, participants could receive a new cycle with efgartigimod, if the following criteria were met: (1) An MG-ADL total score ≥5 points with more than 50% of the total score due to nonocular symptoms, and (2) A reduction in MG-ADL total score of <2 points compared to the score at the corresponding cycle baseline (all participants for the first cycle, comparison was to the previous treatment cycle baseline in ARGX-113-1704).

[d] A participant in Part B of ARGX-113-1705 started another cycle when all of the following criteria were met: (1) The participant completed the previous cycle's treatment period (ie, after visit 4); (2) Treatment with efgartigimod was in the best interest of the participant, according to the investigator; and (3) A minimum of 4 weeks (1 calendar month) had elapsed since the last efgartigimod infusion.

[e] In ARGX-113-2002, total is the combination of SC 2001, IV 2001, and IV 1705 treatment arms from the antecedent studies.

[f] In ARGX-113-2002, SC 2001 refers to participants who received efgartigimod PH20 SC in both ARGX-113-2001 and ARGX-113-2002.

[g] In ARGX-113-2002, IV 2001 refers to participants who received efgartigimod IV in ARGX-113-2001 and efgartigimod PH20 SC in ARGX-113-2002.

[h] In ARGX-113-2002, IV 1705 refers to participants who received efgartigimod IV in ARGX-113-1705 and efgartigimod PH20 SC in ARGX-113-2002.

[i] In ARGX-113-2002, total IV refers to the combination of IV 2001 and IV 1705 treatment arms.

[j] In ARGX-113-1705, the efgartigimod-efgartigimod cohort refers to participants who received efgartigimod IV in the antecedent study ARGX-113-1704 and efgartigimod IV in the extension study ARGX-113-1705.

[k] In ARGX-113-1705, the placebo-efgartigimod cohort refers to participants who received placebo in the antecedent study ARGX-113-1704 and efgartigimod IV in the extension study ARGX-113-1705.

[l] In ARGX-113-1705, total efgartigimod is a combination of the efgartigimod-efgartigimod and placebo-efgartigimod cohorts.

[m] AChR-Ab status was determined by serology at screening.

[n] In ARGX-113-1704, a participant was considered an MG-ADL responder if there was a ≥2-point reduction in the MG-ADL total score compared to first cycle baseline and it was maintained for the next 4 consecutive weeks (ie, 5 consecutive visits total), with the first reduction occurring no later than 1 week after the previous infusion in a cycle.

[o] In ARGX-113-2001, the AUEC of the percent reduction from baseline total IgG and AChR-Ab and similar AUEC for each IgG subtype was determined at the following dosing intervals: baseline to week 1, week 1 to 2, week 2 to 3, week 3 to 4, baseline to week 4, baseline to week 8, and baseline to week 10.

Supportive Study ARGX-113-2002 (Phase 3 Open-Label Extension of Studies ARGX-113-2001 and ARGX-113-1705) Interim Analysis 1

ARGX-113-2002 is an ongoing study that enrolled participants from ARGX-113-2001 or ARGX-113-1705 (refer to Table 1 above for details). The first IA of ARGX-113-2002 includes all participants who received treatment with efgartigimod PH20 SC by the time of the data cutoff date (March 2, 2022). Data from ARGX-113-2002 provide supportive evidence of the efficacy of efgartigimod PH20 SC for up to 5 cycles.

Main inclusion/exclusion criteria included (among others):

- Previously participated in antecedent studies ARGX-113-2001 or ARGX-113-1705 and are eligible for rollover as defined by:

  a. For ARGX-113-2001

  - Completed the study and performed the EoS visit, or
  - Were discontinued from study treatment for reasons other than pregnancy or an (S)AE. Receiving rescue therapy is not exclusionary unless given in a response to a life-threatening situation

  b. For ARGX-113-1705

  - Performed the end of part A, or

- Started Part B, received the previous dose of efgartigimod IV at least 30 days prior to entry into this study, completed at least 1 year of study ARGX-113-1705, and performed the early discontinuation visit in ARGX-113-1705
- Did not have 3 consecutive treatment failures in ARGX-113-1705 Part A, even if the participant received rescue therapy (unless rescue therapy was given in response to a life-threatening situation). Treatment failure is defined as the absence of a decrease of at least 2 points in total MG-ADL score compared to the subsequent TP baseline in at least 50% of the assessments
- Are still receiving concomitant gMG medication. Participants who have stopped taking any concomitant medication for gMG are not eligible for rollover
- Participants may rollover from ARGX-113-1705 until recruitment for this study is closed

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

- The participant was discontinued early from studies ARGX-113-2001 or ARGX-113-1705, unless the reason for discontinuation from study ARGX-113-1705 was to rollover into study ARGX-113-2002

  a. Participants who, in the investigator's judgment, are not benefiting from efgartigimod IV in study ARGX-113-1705 Part B are not eligible for rollover into ARGX-113-2002

As of the cutoff date, a total of 178 participants rolled over to ARGX-113-2002 from the antecedent studies ARGX-113-2001 and ARGX-113-1705. Of these, 53 participants received efgartigimod PH20 SC in ARGX-113-2001, 52 participants received efgartigimod IV in ARGX-113-2001, and 73 participants received efgartigimod IV in ARGX-113-1705. Of the 178 participants enrolled in this study, 164 participants received efgartigimod PH20 SC and are defined as the total group.

Overall, 4 (2.4%) participants discontinued treatment, and 160 (97.6%) participants were still ongoing.

In the total group, the mean (SD) study duration was 169.7 (58.82) days. The mean (SD) duration of all cycles combined, was 160.6 (60.17) days, which resulted in 72.1 patient-years of follow-up. The median (min, max) duration of all cycles combined was 172.5 (7, 311) days.

A treatment period and its corresponding intertreatment period were grouped into cycles for analysis. Median cycle durations were 56.0 days for C1, 56.0 days for C2, 50.0 days for C3, and 50.0 days for C4, with the maximum cycle duration of C1 reaching up to 204 days. Overall, most participants (65.1%, 75.2%, 86.8%, and 96.0% in C1, C2, C3, and C4, respectively) had a cycle duration of 7 weeks, which aligns with the protocol-specified minimum duration of a cycle.

The majority of participants were AChR-Ab seropositive (81.7%). The median age was 50.0 years and most participants were White (89.6%) and female (64.6%). A total of 14 (8.5%) participants were Japanese.

In the AChR-Ab seropositive population, the maximum MG-ADL total score reduction from cycle baseline decreased with subsequent cycles because the cycle baseline MG-ADL total score decreased with subsequent cycles (Figure below). MG-ADL total scores did not return to study baseline levels before initiation of the next cycle because participants were retreated based on the investigator's judgment rather than a specific MG-ADL total score threshold. The mean (SE) change from study baseline in MG-ADL total score in the total group at week 4 in the AChR-Ab seropositive population was −4.1 (0.29) in C1, −4.0 (0.32) in C2, −4.2 (0.35) in C3, and −4.6 (0.46) in C4 (figure below).

Figure 35: Study ARGX-113-2002 IA1: Mean (SE) Change From Study Baseline in MG-ADL Total Score Over Time for the First 4 Cycles in the AChR-Ab Seropositive Population (Safety Analysis Set)

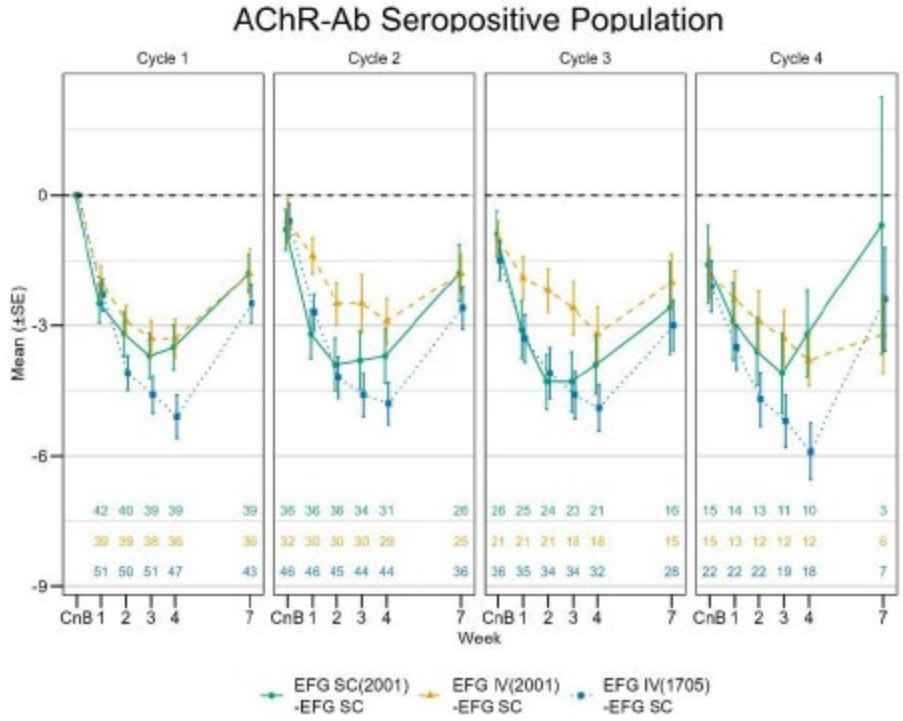


Table 25: MD-ADL descriptive statistics of actual values and changes from baseline and cycle baseline in MG-ADL total score by AChR-Ab status

ANALYSIS SET: SAFETY

AChR-Ab STATUS: POSITIVE

	EFG SC (2001) - EFG SC (N=42)	EFG IV (2001) - EFG SC (N=39)	EFG IV (1705) - EFG SC (N=53)	TOTAL EFG IV - EFG SC (N=92)	TOTAL (N=134)
CYCLE 1					
CYCLE BASELINE					
ACTUAL VALUES					
n	42	39	53	92	134
Mean (S.E.)	6.8 (0.55)	6.8 (0.45)	8.8 (0.48)	8.0 (0.35)	7.6 (0.30)
95% C.I.	(5.73; 7.94)	(5.87; 7.72)	(7.88; 9.82)	(7.28; 8.68)	(7.03; 8.21)
Median	7.0	7.0	9.0	7.5	7.0
Q1; Q3	(5.0; 9.0)	(5.0; 9.0)	(6.0; 11.0)	(6.0; 10.0)	(5.0; 10.0)
Min; Max	(0; 14)	(1; 13)	(2; 20)	(1; 20)	(0; 20)
CYCLE 1					
WEEK 1					
ACTUAL VALUES					
n	42	39	51	90	132
Mean (S.E.)	4.3 (0.47)	4.8 (0.46)	6.6 (0.48)	5.8 (0.35)	5.3 (0.29)
95% C.I.	(3.37; 5.25)	(3.89; 5.75)	(5.65; 7.57)	(5.14; 6.52)	(4.78; 5.91)
Median	4.0	5.0	6.0	6.0	5.0
Q1; Q3	(2.0; 7.0)	(2.0; 7.0)	(5.0; 9.0)	(3.0; 7.0)	(3.0; 7.0)
Min; Max	(0; 10)	(0; 12)	(0; 15)	(0; 15)	(0; 15)
CHANGES FROM BASELINE					
n	42	39	51	90	132
Mean (S.E.)	-2.5 (0.45)	-2.0 (0.37)	-2.3 (0.37)	-2.2 (0.26)	-2.3 (0.23)
95% C.I.	(-3.44; -1.61)	(-2.72; -1.23)	(-3.08; -1.59)	(-2.70; -1.65)	(-2.74; -1.83)
Median	-1.5	-2.0	-2.0	-2.0	-2.0
Q1; Q3	(-4.0; -1.0)	(-3.0; 0.0)	(-4.0; -1.0)	(-4.0; -1.0)	(-4.0; -1.0)
Min; Max	(-12; 2)	(-11; 1)	(-8; 9)	(-11; 9)	(-12; 9)
CHANGES FROM CnB					
n	42	39	51	90	132
Mean (S.E.)	-2.5 (0.45)	-2.0 (0.37)	-2.3 (0.37)	-2.2 (0.26)	-2.3 (0.23)
95% C.I.	(-3.44; -1.61)	(-2.72; -1.23)	(-3.08; -1.59)	(-2.70; -1.65)	(-2.74; -1.83)
Median	-1.5	-2.0	-2.0	-2.0	-2.0
Q1; Q3	(-4.0; -1.0)	(-3.0; 0.0)	(-4.0; -1.0)	(-4.0; -1.0)	(-4.0; -1.0)
Min; Max	(-12; 2)	(-11; 1)	(-8; 9)	(-11; 9)	(-12; 9)

CYCLE 1

WEEK 4

ACTUAL VALUES					
n	39	36	47	83	122
Mean (S.E.)	3.2 (0.41)	3.4 (0.45)	3.8 (0.41)	3.6 (0.30)	3.5 (0.24)
95% C.I.	(2.38; 4.03)	(2.47; 4.31)	(3.01; 4.65)	(3.04; 4.24)	(3.02; 3.98)
Median	3.0	3.0	4.0	3.0	3.0
Q1; Q3	(1.0; 5.0)	(1.0; 5.0)	(2.0; 6.0)	(2.0; 6.0)	(1.0; 5.0)
Min; Max	(0; 10)	(0; 10)	(0; 10)	(0; 10)	(0; 10)
CHANGES FROM BASELINE					
n	39	36	47	83	122
Mean (S.E.)	-3.5 (0.51)	-3.3 (0.44)	-5.1 (0.49)	-4.3 (0.35)	-4.1 (0.29)
95% C.I.	(-4.57; -2.51)	(-4.22; -2.45)	(-6.09; -4.13)	(-5.03; -3.65)	(-4.65; -3.51)
Median	-3.0	-3.0	-5.0	-4.0	-4.0
Q1; Q3	(-5.0; -1.0)	(-4.5; -1.0)	(-8.0; -2.0)	(-6.0; -2.0)	(-6.0; -2.0)
Min; Max	(-12; 2)	(-11; 0)	(-14; 3)	(-14; 3)	(-14; 3)
CHANGES FROM CnB					
n	39	36	47	83	122
Mean (S.E.)	-3.5 (0.51)	-3.3 (0.44)	-5.1 (0.49)	-4.3 (0.35)	-4.1 (0.29)
95% C.I.	(-4.57; -2.51)	(-4.22; -2.45)	(-6.09; -4.13)	(-5.03; -3.65)	(-4.65; -3.51)
Median	-3.0	-3.0	-5.0	-4.0	-4.0
Q1; Q3	(-5.0; -1.0)	(-4.5; -1.0)	(-8.0; -2.0)	(-6.0; -2.0)	(-6.0; -2.0)
Min; Max	(-12; 2)	(-11; 0)	(-14; 3)	(-14; 3)	(-14; 3)

	EFG SC (2001) - EFG SC (N=42)	EFG IV (2001) - EFG SC (N=39)	EFG IV (1705) - EFG SC (N=53)	TOTAL EFG IV - EFG SC (N=92)	TOTAL (N=134)

CYCLE 1

WEEK 7

ACTUAL VALUES					
n	39	36	43	79	118
Mean (S.E.)	5.2 (0.53)	4.9 (0.66)	6.1 (0.51)	5.6 (0.41)	5.4 (0.33)
95% C.I.	(4.14; 6.27)	(3.60; 6.29)	(5.04; 7.10)	(4.74; 6.38)	(4.80; 6.08)
Median	5.0	4.0	6.0	5.0	5.0
Q1; Q3	(3.0; 7.0)	(1.5; 7.0)	(3.0; 8.0)	(3.0; 8.0)	(3.0; 7.0)
Min; Max	(0; 14)	(0; 16)	(0; 15)	(0; 16)	(0; 16)
CHANGES FROM BASELINE					
n	39	36	43	79	118
Mean (S.E.)	-1.8 (0.44)	-1.8 (0.56)	-2.5 (0.45)	-2.2 (0.35)	-2.1 (0.28)
95% C.I.	(-2.74; -0.95)	(-2.95; -0.66)	(-3.40; -1.58)	(-2.88; -1.47)	(-2.62; -1.52)
Median	-2.0	-2.0	-2.0	-2.0	-2.0
Q1; Q3	(-4.0; 0.0)	(-4.0; 0.0)	(-5.0; 0.0)	(-4.0; 0.0)	(-4.0; 0.0)
Min; Max	(-10; 3)	(-8; 9)	(-9; 7)	(-9; 9)	(-10; 9)
CHANGES FROM CnB					
n	39	36	43	79	118
Mean (S.E.)	-1.8 (0.44)	-1.8 (0.56)	-2.5 (0.45)	-2.2 (0.35)	-2.1 (0.28)
95% C.I.	(-2.74; -0.95)	(-2.95; -0.66)	(-3.40; -1.58)	(-2.88; -1.47)	(-2.62; -1.52)
Median	-2.0	-2.0	-2.0	-2.0	-2.0
Q1; Q3	(-4.0; 0.0)	(-4.0; 0.0)	(-5.0; 0.0)	(-4.0; 0.0)	(-4.0; 0.0)
Min; Max	(-10; 3)	(-8; 9)	(-9; 7)	(-9; 9)	(-10; 9)

CYCLE 1

WEEK 10

ACTUAL VALUES					
n	11	12	15	27	38
Mean (S.E.)	6.0 (1.17)	5.0 (0.79)	6.7 (1.01)	6.0 (0.67)	6.0 (0.58)
95% C.I.	(3.40; 8.60)	(3.27; 6.73)	(4.56; 8.90)	(4.58; 7.34)	(4.81; 7.14)
Median	7.0	5.5	6.0	6.0	6.0
Q1; Q3	(1.0; 9.0)	(3.0; 6.5)	(4.0; 10.0)	(4.0; 8.0)	(4.0; 8.0)
Min; Max	(0; 12)	(1; 9)	(0; 13)	(0; 13)	(0; 13)
CHANGES FROM BASELINE					
n	11	12	15	27	38
Mean (S.E.)	0.0 (0.93)	-0.7 (0.74)	-1.7 (0.86)	-1.2 (0.58)	-0.9 (0.49)
95% C.I.	(-2.08; 2.08)	(-2.30; 0.97)	(-3.51; 0.18)	(-2.41; -0.03)	(-1.87; 0.13)
Median	0.0	-0.5	0.0	0.0	0.0
Q1; Q3	(-1.0; 1.0)	(-2.5; 1.0)	(-4.0; 0.0)	(-3.0; 1.0)	(-2.0; 1.0)
Min; Max	(-7; 6)	(-5; 4)	(-8; 4)	(-8; 4)	(-8; 6)
CHANGES FROM CnB					
n	11	12	15	27	38
Mean (S.E.)	0.0 (0.93)	-0.7 (0.74)	-1.7 (0.86)	-1.2 (0.58)	-0.9 (0.49)
95% C.I.	(-2.08; 2.08)	(-2.30; 0.97)	(-3.51; 0.18)	(-2.41; -0.03)	(-1.87; 0.13)
Median	0.0	-0.5	0.0	0.0	0.0
Q1; Q3	(-1.0; 1.0)	(-2.5; 1.0)	(-4.0; 0.0)	(-3.0; 1.0)	(-2.0; 1.0)
Min; Max	(-7; 6)	(-5; 4)	(-8; 4)	(-8; 4)	(-8; 6)

	EFG SC (2001) - EFG SC (N=42)	EFG IV (2001) - EFG SC (N=39)	EFG IV (1705) - EFG SC (N=53)	TOTAL EFG IV - EFG SC (N=92)	TOTAL (N=134)
CYCLE 2					
CYCLE BASELINE					
ACTUAL VALUES					
n	36	32	46	78	114
Mean (S.E.)	6.2 (0.57)	6.2 (0.65)	7.9 (0.51)	7.2 (0.41)	6.9 (0.33)
95% C.I.	(5.07; 7.37)	(4.88; 7.55)	(6.87; 8.91)	(6.39; 8.02)	(6.23; 7.56)
Median	6.0	6.0	8.0	7.0	6.5
Q1; Q3	(4.0; 8.5)	(4.0; 9.0)	(5.0; 10.0)	(5.0; 9.0)	(5.0; 9.0)
Min; Max	(0; 14)	(0; 16)	(0; 15)	(0; 16)	(0; 16)
CHANGES FROM BASELINE					
n	36	32	46	78	114
Mean (S.E.)	-0.8 (0.46)	-0.6 (0.53)	-0.6 (0.39)	-0.6 (0.32)	-0.7 (0.26)
95% C.I.	(-1.75; 0.14)	(-1.67; 0.48)	(-1.42; 0.16)	(-1.24; 0.01)	(-1.19; -0.16)
Median	-0.5	-1.0	-0.5	-1.0	-1.0
Q1; Q3	(-2.0; 1.0)	(-2.0; 0.5)	(-2.0; 1.0)	(-2.0; 1.0)	(-2.0; 1.0)
Min; Max	(-10; 6)	(-8; 9)	(-6; 7)	(-8; 9)	(-10; 9)
CYCLE 2					
WEEK 4					
ACTUAL VALUES					
n	31	29	44	73	104
Mean (S.E.)	3.3 (0.50)	4.0 (0.54)	3.8 (0.40)	3.8 (0.32)	3.7 (0.27)
95% C.I.	(2.29; 4.35)	(2.87; 5.06)	(2.96; 4.59)	(3.21; 4.49)	(3.16; 4.23)
Median	3.0	4.0	4.0	4.0	3.0
Q1; Q3	(1.0; 5.0)	(1.0; 6.0)	(2.0; 6.0)	(2.0; 6.0)	(1.0; 5.5)
Min; Max	(0; 10)	(0; 11)	(0; 9)	(0; 11)	(0; 11)
CHANGES FROM BASELINE					
n	31	29	44	73	104
Mean (S.E.)	-3.7 (0.63)	-2.9 (0.52)	-4.8 (0.48)	-4.1 (0.37)	-4.0 (0.32)
95% C.I.	(-5.03; -2.45)	(-3.99; -1.87)	(-5.82; -3.87)	(-4.82; -3.34)	(-4.62; -3.35)
Median	-3.0	-3.0	-5.0	-4.0	-4.0
Q1; Q3	(-6.0; -1.0)	(-4.0; -1.0)	(-7.0; -3.0)	(-6.0; -2.0)	(-6.0; -2.0)
Min; Max	(-12; 2)	(-10; 2)	(-12; 4)	(-12; 4)	(-12; 4)
CHANGES FROM CnB					
n	31	29	44	73	104
Mean (S.E.)	-3.0 (0.53)	-1.9 (0.47)	-4.2 (0.49)	-3.3 (0.37)	-3.2 (0.30)
95% C.I.	(-4.11; -1.95)	(-2.88; -0.98)	(-5.17; -3.19)	(-4.03; -2.55)	(-3.81; -2.61)
Median	-3.0	-2.0	-4.0	-4.0	-3.0
Q1; Q3	(-5.0; -1.0)	(-4.0; 0.0)	(-5.5; -2.0)	(-5.0; -1.0)	(-5.0; -1.0)
Min; Max	(-10; 3)	(-6; 4)	(-13; 1)	(-13; 4)	(-13; 4)
CYCLE 3					
CYCLE BASELINE					
ACTUAL VALUES					
n	26	21	36	57	83
Mean (S.E.)	6.1 (0.73)	5.5 (0.73)	6.5 (0.52)	6.1 (0.43)	6.1 (0.37)
95% C.I.	(4.57; 7.58)	(3.96; 6.99)	(5.47; 7.59)	(5.29; 6.99)	(5.39; 6.85)
Median	5.5	5.0	6.0	6.0	6.0
Q1; Q3	(4.0; 8.0)	(3.0; 8.0)	(5.0; 9.0)	(4.0; 9.0)	(4.0; 8.0)
Min; Max	(0; 13)	(1; 14)	(0; 13)	(0; 14)	(0; 14)
CHANGES FROM BASELINE					
n	26	21	36	57	83
Mean (S.E.)	-0.9 (0.52)	-1.0 (0.40)	-1.5 (0.45)	-1.3 (0.32)	-1.2 (0.27)
95% C.I.	(-1.96; 0.19)	(-1.79; -0.12)	(-2.42; -0.58)	(-1.94; -0.66)	(-1.71; -0.63)
Median	0.0	-1.0	-1.0	-1.0	-1.0
Q1; Q3	(-3.0; 0.0)	(-2.0; 0.0)	(-3.5; 0.0)	(-2.0; 0.0)	(-3.0; 0.0)
Min; Max	(-5; 5)	(-4; 2)	(-10; 5)	(-10; 5)	(-10; 5)
CYCLE 3					
WEEK 4					
ACTUAL VALUES					
n	21	18	32	50	71
Mean (S.E.)	2.7 (0.55)	3.2 (0.75)	3.4 (0.46)	3.4 (0.40)	3.2 (0.32)
95% C.I.	(1.57; 3.86)	(1.64; 4.81)	(2.50; 4.38)	(2.56; 4.16)	(2.53; 3.81)
Median	2.0	2.0	3.0	2.5	2.0
Q1; Q3	(1.0; 4.0)	(0.0; 5.0)	(1.5; 5.0)	(1.0; 5.0)	(1.0; 5.0)
Min; Max	(0; 10)	(0; 10)	(0; 9)	(0; 10)	(0; 10)
CHANGES FROM BASELINE					
n	21	18	32	50	71
Mean (S.E.)	-3.9 (0.68)	-3.2 (0.62)	-4.9 (0.53)	-4.3 (0.42)	-4.2 (0.35)
95% C.I.	(-5.31; -2.50)	(-4.54; -1.91)	(-5.98; -3.83)	(-5.14; -3.46)	(-4.89; -3.48)
Median	-4.0	-3.0	-4.5	-4.0	-4.0
Q1; Q3	(-6.0; -1.0)	(-5.0; -1.0)	(-7.0; -3.0)	(-7.0; -2.0)	(-6.0; -2.0)
Min; Max	(-10; 1)	(-8; 2)	(-11; 1)	(-11; 2)	(-11; 2)
CHANGES FROM CnB					
n	21	18	32	50	71
Mean (S.E.)	-3.2 (0.64)	-2.5 (0.65)	-3.0 (0.45)	-2.8 (0.37)	-2.9 (0.32)
95% C.I.	(-4.53; -1.85)	(-3.87; -1.13)	(-3.95; -2.11)	(-3.58; -2.10)	(-3.58; -2.30)
Median	-2.0	-2.0	-3.0	-3.0	-3.0
Q1; Q3	(-5.0; -1.0)	(-5.0; 0.0)	(-4.5; -1.0)	(-5.0; -1.0)	(-5.0; -1.0)
Min; Max	(-10; 0)	(-7; 2)	(-10; 1)	(-10; 2)	(-10; 2)

Feasibility of Self-Administration of Efgartigimod PH20 SC

Per protocol, efgartigimod may have been administered at home. When efgartigimod administration was performed at home, the associated visit was performed by phone.

Of the total number of efgartigimod PH20 SC administrations, 42.8% were performed by site staff on-site, 30.5% were performed by the participant at home, 24.8% were performed by the participant on-site, 0.8% were performed by the caregiver at home, and 0.9% were performed by the caregiver on-site. By the second treatment visit of C4, >70% of the participants performed self-administration at home, with 47 (72.3%) participants, 45 (71.4%) participants, and 43 (76.8%) participants doing so at visits 2, 3, and 4 of C4, respectively.

ARGX-113-1705-IA4 (31 Jan 2022)

Supportive efficacy results were reported for up to 17 cycles of efgartigimod IV in ARGX-113-1705.

151 participants rolled over to ARGX-113-1705. Overall, 91 (62.8%) participants have discontinued treatment, including 56 (38.6%) participants who enrolled in the open-label ARGX-113-2002 to receive efgartigimod PH20 SC; thus, 35 (24.1%) participants discontinued efgartigimod treatment. A total of 15 (10.3%) participants completed the study. The study is ongoing.

The mean (SD) duration of treatment combined with follow-up was 548.0 (231.79) days, which results in 217.55 patient-years of observation. The median (min, max) study duration with follow-up was 588.0 (40, 924) days. Treatment combined with follow-up was <6 months for 14 (9.7%) participants, 6 to <12 months for 18 (12.4%) participants, 12 to <18 months for 23 (15.9%) participants, 18 to <24 months for 49 (33.8%) participants, 24 to <30 months for 38 (26.2%) participants, and 30 to <36 months for 3 (2.1%) participants.

Median cycle durations for the first 16 cycles of efgartigimod IV in ARGX-113-1705 (50.0-68.0 days: Module 5.3.5.2, ARGX-113-1705-IA4 CSR, Table 14.1.1.5.3) were similar to median cycle durations for the first 4 cycles of efgartigimod PH20 SC in ARGX-113-2002 (50.0-56.0 days), indicating consistency of efficacy after switching from efgartigimod IV to efgartigimod PH20 SC.

The mean (SE) change from cycle baseline in the MG-ADL total score in the total efgartigimod AChR-Ab seropositive population observed at week 3 was −5.0 (0.33) in C1, −5.3 (0.36) in C2, −5.3 (0.37) in C3, −5.9 (0.42) in C4, −5.8 (0.40) in C5, −5.6 (0.43) in C6, −6.4 (0.48) in C7, −6.4 (0.50) in C8, −7.2 (0.49) in C9, −7.5 (0.65) in C10, −5.7 (0.88) in C11, −6.7 (0.72) in C12, −6.1 (0.94) in C13, and −5.2 (1.08) in C14.

In the AChR-Ab seropositive population, in the majority of cycles (11 out of 14) and including the first 10 cycles, >90% of participants had a minimum improvement from cycle baseline of ≥2 points in the MG-ADL total score.

2.5.6. Discussion on clinical efficacy

The subject of this submission is a line extension request to the Vyvgart marketing authorization for a new pharmaceutical form (solution for injection) associated with a new strength (1 000 mg) and a new route of administration (subcutaneous use): Vyvgart 1 000 mg, solution for injection).

The dose is 1000 mg administered SC in cycles of once-weekly injections for 4 weeks. The frequency of treatment cycles with efgartigimod PH20 SC may vary by patient. Subsequent treatment cycles will be administered according to clinical evaluation.

The main evidence for demonstration of the efficacy of IV formulation was based on data from a single 26-week, randomised, placebo-controlled Phase 3 clinical trial (Study ARGX-113-1704) which included mainly two cycles of treatment. The maintenance of the effect (beyond the initial one to three cycles) was based on available results from the ongoing open label study (Study ARGX-113-1705, data cut-off date 01 February 2021) with an intended duration of 3 years and was limited to analyses of MG-ADL changes (different definition and timing from primary endpoint in pivotal study).

ARGX-113-2001 is considered the main study for this application (for SC administration), while data from ARGX-113-2002 is supportive for maintenance of effect or safety profile after the first cycle.

There are no specific CHMP guidelines for myasthenia gravis therapeutic area or for formulation change in treatment of this population. Study ARGX-113-2001 was conducted as a confirmatory trial and is acceptable for the purpose of showing "therapeutic equivalence" of the two formulations despite some concerns discussed below.

Design and conduct of clinical studies

To bridge the results of the placebo-controlled study ARGX-113-1704 (using efgartigimod IV) to the SC formulation, ARGX-113-2001, a phase 3, randomized, 12-week open-label study with PD, PK, efficacy, safety, tolerability, and immunogenicity endpoints was conducted in participants with gMG to show therapeutic equivalence of SC and IV formulations during 1 clinical cycle (includes 4 weekly administrations and follow up).

Main inclusion/exclusion criteria are resembling the criteria for the pivotal study for iv formulation (ARGX-113-1704). The inclusion criteria are specific for gMG limiting the population to symptomatic patients with confirmed diagnosis, and together with exclusion criteria can generally be considered suitable to define a relevant patient population; however, with some limitations. Eligible subjects were males or females, aged 18 years or older, with confirmed diagnosis of MG (determined by electrophysiological/ pharmacological confirmation) and symptomatic generalized MG (who are defined as patients with MG-ADL total score of ≥5 points at screening and baseline with >50% of the total score attributed to non-ocular symptoms, but not in manifest myasthenic crisis, so MGFA class II, III, IVa, or IVb were enrolled).

It is critical to keep in mind that efgartigimod treatment is not indicated for patients in impending or manifest mysthenic crisis (a serious, life-threatening, rapid worsening of MG and potential airway compromise from ventilatory or bulbar dysfunction). The use of efgartigimod is significantly different from the use of IVIg or PLEX treatments which are appropriately used as: short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations; and when other treatments are insufficiently effective. Efgartigimod is not replacing IVIg or PLEX use in MGFA Class V patients and this is reflected clearly in the SmPC.

Both AChR-Ab seropositive and negative, or newly diagnosed and previously treated patients were enrolled. This is not in line with the existing indication for IV formulation as it is limited to AChR-Ab seropositive population. Efgartigimod was administered on top of stable background therapy (eg, NSIDs, steroids, and AChE inhibitors). Rescue therapy (PLEX, IVIg, immunoadsorption, new type or increased dose of corticosteroid) was permitted and resulted in discontinuation of the patient from the randomised treatment. Abdominal skin tissue was evaluated by the investigator to allow for absorption and assessment of local safety of the planned SC injection, but this criterion did not lead to exclusion of patients from screening.

Patients were excluded if they had received any monoclonal antibody in the 6 months before IMP, undergone thymectomy within 3 months, had IV/SC/IM immunoglobulin or plasma exchange within 1 month of screening. In addition to concomitant or previous therapy, the exclusion criteria mainly addressed autoimmune diseases, infections and malignancy risk. Patients were excluded if they had documentation of a lack of clinical response to PLEX or had serum IgG levels less than 6 g/L at screening. Patients with worsening muscle weakness secondary to concurrent infections or medications (aminoglycosides, beta-blockers, etc.), and who received a live-attenuated vaccine within the last 4 weeks prior to screening or were pregnant were excluded. The relevant warnings are inserted in SmPC.

It is important to note that IV formulation has a weight-based dosing (10 mg/kg per infusion) up to 120kg, while SC formulation is a fixed dose for all weight ranges. However, weight-PD relationship is not established.

A total of 111 participants were enrolled and randomized in a 1:1 ratio to receive either efgartigimod PH20 SC 1000 mg or efgartigimod IV 10 mg/kg once weekly for 4 administrations at 43 international sites (in 11 countries): 55 participants in SC arm and 56 participants in IV arm. One participant was randomized to the efgartigimod IV arm but did not receive efgartigimod due to an AE (pyrexia). There were 110 participants (55 in each arm) in all analysis sets (safety, ITT, mITT) which reflected all randomized participants who were exposed to the IMP or with a value for total IgG levels at baseline and at least 1 postbaseline time point. 80 patients (73%) were enrolled in Europe, Georgia and Russia the population is considered as representative of patients in EU. Randomization was stratified by Japanese versus non-Japanese participants. Within non-Japanese participants, randomization was further stratified by AChR-Ab status. In total 91 AChR-Ab seropositive patients were treated, 45 in SC and 46 in IV arm.

The median age was 53.5 years (range: 19 to 84 years), with more of the participants across both arms in the 18 to <65 years age category (80 [72.7%]) and female dominance (65 [59.1%]). A total of 8 (7.3%) participants met the definition of a Japanese participant.

At entry, the majority of patients were concomitantly treated with anticholinesterases (86.4%), steroids (66.4%), and NSIDs (43.6%) and no changes were allowed during the study. 69.1 % had at least 2 prior therapies, and 30% of patients had at least 3 prior therapies. The most frequently reported MGFA class at screening was Class III in 54 (49.1%) patients followed by Class II in 51 (46.3%) patients, indicative of a symptomatic patient population with mild to moderate weakness affecting muscles other than the ocular muscles (but still a milder population in terms of background therapies and MGFA class than the pivotal study for IV formulation). The mean baseline MG-ADL (8.7) and QMG (15.2) scores demonstrate substantial disease burden despite ongoing generalised myasthenia gravis treatment. Overall, 107 (97.3%) patients completed treatment and 108 (98.2%) patients completed the study. Treatment compliance was 100% for IV arm while it went down to 89.1% for SC arm. There were slight imbalances between treatment arms in terms of demographics and disease characteristics, which are not considered significant as differences largely balance out each other not to favour one arm overall.

PD noninferiority and clinical endpoints are used to show therapeutic equivalence of SC and IV formulations. The bridging approach is based on the association between reductions in both total IgG and AChR-Ab levels and improvement in the MG-ADL total score. The primary objective of this study was to demonstrate the NI of the SC formulation compared with the IV formulation in treating participants with gMG using total IgG percent reduction at day 29 based on an NI margin of 10%-points. The primary endpoint was analysed using an ANCOVA model with treatment as a factor and total IgG levels at baseline as a covariate. With a NI margin of 10%-points in total IgG percent reduction, 84% (1–10/62.2×100%) of the PD effect was expected to be preserved. The primary endpoint is not considered adequate on its own to demonstrate therapeutic equivalence of two formulations. Total IgG reduction as a PD biomarker is not mechanistically linked to the disease but the

reduction of AChR-Ab levels could be linked for AChR-Ab seropositive gMG population. The comparison of percent reductions from baseline in AChR-Ab levels at day 29 between two formulations was included as post-hoc analysis. It was analysed using an ANCOVA model with treatment as a factor and baseline AChR-Ab levels as a covariate in AChR-Ab seropositive participants in the mITT analysis (similar to the ANCOVA analysis of the primary endpoint). The p-value for testing the same null hypothesis of NI as specified in the protocol is provided.

The secondary endpoints included PD, PK, efficacy, safety/tolerability, immunogenicity assessments while the exploratory endpoints were evaluating self-administration. The secondary and exploratory endpoints were summarized with descriptive statistics by treatment arm and overall among all participants, and reflected this way in the SmPC. Upon request, the presentation of primary or secondary endpoints in SmPC reflects the indication sought (AChR-Ab seropositive subpopulation, mITT). It is different from ARGX-113-1704 study where the primary analysis was based on AChR-Ab seropositive population.

Secondary clinical efficacy endpoints used the scales which were used in the pivotal study for the iv formulation and this allows indirect comparison of changes in total scores over time or percentage of responders (especially for MG-ADL and QMG scales). The selected clinical scales are validated standard methods for evaluation of MG and have been previously used in several clinical studies in this condition. Based on data from C1 to C3 of ARGX-113-1704, the association between the average AUEC of percent total IgG reduction on the MG-ADL response was shown to be highly significant in the AChR-Ab seropositive population. The model for NI margin predicted a loss of 3% to 4% clinical efficacy in terms of MG-ADL response, with a 10% less decrease in the average AUEC of percent IgG reduction between the baseline to week 4. In the worst-case scenario, on MG-ADL responder rate, the change of 95% confidence interval for the difference of IV-placebo (20.6% observed in ARGX-113-1704 Study) and the predicted SC-placebo would be around 3%. This treatment effect size is considered marginal but acceptable as a lower boundary.

There are no specific CHMP guidelines for myasthenia gravis therapeutic area or for demonstrating therapeutic equivalence in treatment of this population to support the choice of 10% NI margin. However, the issue is not pursued further as the data from ARGX-113-2001 is promising and that requesting a more thorough justification of the relevance of the current non-inferiority margin as opposed to other choices is not considered of value.

Clinical efficacy analyses were performed on the ITT analysis set. Sensitivity analyses on the possible impact due to treatment discontinuation, use of excluded concomitant medication or missed doses was done within the estimand frame, using imputation strategies for missing values based on missing at random assumption, as well as missing not at random. Based from this, it was concluded that the estimated treatment difference was very robust with very little impact due to these intercurrent events.

Study ARGX-113-2002

After completing ARGX-113-2001, participants had the option to roll over to ARGX-113-2002. ARGX-113-2002 is an ongoing study evaluating the long-term safety and efficacy of efgartigimod PH20 SC in participants who rolled over from either ARGX-113-2001 (in which they may have received efgartigimod IV or efgartigimod PH20 SC) or ARGX-113-1705 (in which all participants received efgartigimod IV). As of the first interim analysis data cutoff date (March 2, 2022) included in this submission, participants have completed up to 5 cycles of treatment with efgartigimod PH20 SC according to clinical evaluation.

A total of 178 participants rolled over to ARGX-113-2002: 73 participants who previously received efgartigimod IV in ARGX-113-1705; and from ARGX-113-2001, 53 participants who received SC and 52 participants who received IV treatment. 164 of these participants received efgartigimod PH20 SC in ARGX-113-2002 and are defined as the total group. 4 (2.4%) participants discontinued treatment. Median cycle durations were 56.0

days for C1, 56.0 days for C2, 50.0 days for C3, and 50.0 days for C4, with the maximum cycle duration of C1 reaching up to 204 days. Overall, most participants (65.1%, 75.2%, 86.8%, and 96.0% in C1, C2, C3, and C4, respectively) had a cycle duration of 7 weeks, which aligns with the protocol-specified minimum duration of a cycle. The majority of participants were AChR-Ab seropositive (81.7%).

Exclusion of patients who did not respond to efgartigimod treatment or had life-threatening events limits the translation of the results to the future real-life experience. Only MG-ADL scores, not QMG, were collected in follow up study. Being aware of the limitations, the data is assessed as supportive evidence for maintenance of efficacy beyond first cycle with SC formulation.

Efficacy data and additional analyses

Study ARGX-113-2001

The primary endpoint was met in study ARGX-113-2001, meaning that the percent reduction from baseline in total IgG levels at day 29 in participants with gMG who received SC formulation was NI to that in participants who received IV formulation after 1 treatment cycle of 4 weekly administrations (refer to the Clinical Pharmacology section for details). Results for total IgG levels at day 29 were consistent when analysed for the AChR-Ab seropositive population in the mITT analysis set.

Decreases in AChR-Ab levels followed a comparable time course as total IgG levels in AChR-Ab positive patients. Maximum mean percentage decreases in AChR-Ab levels of 62.2% and 59.6% were observed one week after the last administration in the efgartigimod alfa subcutaneous and intravenous groups, respectively. As the primary endpoint on total IgG levels cannot be mechanistically linked to the disease, and the exposure-response relationship might be different for pathogenic antibodies, AChR-Ab levels (pathogenic IgG) are considered the most important to show therapeutic equivalence.

For both the efgartigimod alfa subcutaneous and intravenous groups, decrease in total IgG and AChR-Ab levels were associated with and preceded a clinical response in AChR-Ab positive patients. The clinical efficacy of efgartigimod PH20 SC, using validated clinical outcome scales including the participant-reported MG-ADL scale (subjective assessment of MG symptoms) and the physician-assessed QMG scale (quantitative evaluation of relevant muscle groups), was similar to the clinical efficacy of efgartigimod IV showing similar decrease in functional disability. In line with the sought indication for SC formulation, assessment of CHMP on clinical results are focused to AChR-Ab seropositive group only, disregarding overall population in clinical efficacy evaluation.

During first treatment cycle in the AChR-Ab seropositive population, the MG-ADL responder criterion (based on a reduction of ≥2 points from baseline on the MG-ADL score for ≥4 consecutive weeks) was met in 71.1% and 71.7% for participants in SC and IV arms, respectively (32 and 33 participants). The maximum reduction in MG-ADL total score was at week 4; the mean change from baseline at week 4 was −5.3 (0.42) versus −4.6 (0.38) ([95% CI: −1.83 to 0.41]) in SC and IV arms, respectively. At week 10 (end of the study), the mean (SE) change from baseline in MG-ADL total score was −2.4 (0.52) versus −2.2 (0.49) in SC and IV arms, respectively. A 2-point reduction in MG-ADL total score can be considered as clinically meaningful and this was achieved and maintained for both groups in the first cycle. (As an indirect reference, in pivotal study for IV formulation, ARGX-113-1704, the mean (95% CI) change from baseline in the MG-ADL total score was -4.104 (-5.007; -3.201) points in the efgartigimod group and -1.269 (-2.199; -0.339) points in the placebo group.)

The percentage of QMG responders for the AChR-Ab seropositive population (based on a reduction of ≥3 points from baseline on the QMG score for ≥4 consecutive weeks) was 68.9% and 53.3% for participants in SC and IV arms, respectively. The maximum reduction in QMG total score was at week 4; the mean QMG change from

baseline at week 4 was −6.5 (0.70) versus −5.4 (0.53) in SC and IV arms, respectively. At week 10 (end of the study), the mean (SE) change from baseline in QMG total score was −2.5 (0.70) versus −2.7 (0.61) in SC and IV arms, respectively. A 3.5-point difference has been shown to correlate with clinically meaningful change in QMG and this had been achieved at week 4 but was not maintained until week 10.

Sensitivity analyses on the possible impact due to treatment discontinuation, use of excluded concomitant medication or missed doses was done within the estimand frame, using imputation strategies for missing values based on missing at random assumption, as well as missing not at random. Based from this, it was concluded that the estimated treatment difference was very robust with very little impact due to these intercurrent events.

Overall, two efgartigimod formulations have demonstrated a similar and clinically relevant efficacy in treatment of AChR-Ab seropositive population in one treatment cycle in study ARGX-113-2001, as rated by patients (MG-ADL) and physicians (QMG).

Decreases in AChR-Ab levels followed a comparable time course as total IgG levels (and preceded a clinical response) in AChR-Ab positive patients and were similar between the SC and IV groups. Maximum mean percentage decreases in AChR-Ab levels of 62.2% and 59.6% were observed one week after the last administration in SC and IV groups, respectively.

Study ARGX-113-2002

In the AChR-Ab seropositive population, the maximum MG-ADL total score reduction from cycle baseline decreased with subsequent cycles, because participants were retreated based on the investigator's judgment rather than a specific MG-ADL total score threshold. The mean (SE) change from study baseline in MG-ADL total score in the total group at week 4 in the AChR-Ab seropositive population was −4.1 (0.29) in C1, −4.0 (0.32) in C2, −4.2 (0.35) in C3, and −4.6 (0.46) in C4.

In all 4 cycles, the MG-ADL improvements were at clinically meaningful level but demonstrated some differences between cycles and groups. For the participants who received efgartigimod IV in ARGX-113-2001 and efgartigimod PH20 SC in ARGX-113-2002, the MG-ADL improvements seem to be less and delayed compared to other two groups. The participants who received efgartigimod IV in ARGX-113-1705 and efgartigimod PH20 SC in ARGX-113-2002 are in EFG IV(1705)-EFG SC group and have the best results. Better response in EFG IV(1705)-EFG SC group could be influenced by selection bias as patients who were not benefiting from efgartigimod IV in study ARGX-113-1705 were not allowed to switch to ARGX-113-2002 study hence the SC formulation. The variability in MG-ADL improvements reached 1.9 points at week 4 for cycle 2 and 1.7 points at week 4 for cycle 3. Cycle 4 had data from 10 to 18 patients in each group, so was relatively limited. The variability is explained by the baseline differences and the treatment cycle difference.

Self-administration in Study ARGX-113-2001 and ARGX-113-2002

The first dose of efgartigimod PH20 SC was to be administered by the investigator. According to the protocol, participants/caregivers could have administered subsequent doses after they were trained in administration. During study ARGX-113-2001, although 54 out of 55 participants in SC arm completed the self-administration/ caregiver-supported administration training, only 42 (76.4%) were considered adequately trained for self-administration even after receiving up to 9 training visits. Afterwards, this situation did not improve much during open label follow up study. Although ARGX-113-2002 is a follow up study and a high dropout rate was observed, still only 31.3% of the administrations were performed by the participants/caregivers at home. The low number of self-administrations despite many training attempts during both studies are concerning. The MAH clarified that participants who received efgartigimod IV during the antecedent study were no allowed to self-administer efgartigimod PH20 SC at home during the first treatment cycle in ARGX-113-2002. Additionally,

the first injection of each treatment period was required to be performed on site for operational reasons. The MAH used SmPC/PL material for training on self-administration. A demonstration of proper self-administration under supervision of healthcare professional is considered necessary during training. The first treatment cycle and first injection of the second treatment cycle is required to be performed by or under the supervision of a healthcare professional. Subsequent treatment should be administered by a healthcare professional or may be administered by a patient or caregiver after adequate training in the subcutaneous injection technique. Guidance text has been added to the SmPC.

2.5.7. Conclusions on the clinical efficacy

Overall, in study ARGX-113-2001, SC and IV efgartigimod formulations (as add-on to standard therapy) have demonstrated a similar and clinically relevant efficacy in treatment of AChR-Ab seropositive population in one treatment cycle, as rated by patients and physicians and by total IgG reduction at day 29. This was supported by results from study ARGX-113-2002 for up to 4 cycles. Although primary PD and secondary clinical endpoints were met, the primary endpoint cannot be accepted to show therapeutic equivalence directly. The totality of evidence is considered to support therapeutic equivalence of IV and SC formulations of efgartigimod.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

In the following assessment the two studies ARGX-113-2001 and ARGX-113-2002 as well as SC pooling block will be used as the main clinical safety database. The phase 1 studies will be used as supportive safety data and will be included where considered appropriate. The IV studies and IV pooling block will be used for comparisons to identify any clinically meaningful differences in the safety profile between efgartigimod alfa IV and efgartigimod PH20 SC and to support the long-term safety of efgartigimod PH20 SC.

Studies ARGX-113-2001 and ARGX-113-2002

In ARGX-113-2001, in the overall population (including AChR-Ab seropositive and negative participants), 111 participants were enrolled and randomized to receive the investigational medical product: 55 participants in the efgartigimod PH20 SC arm and 56 participants in the efgartigimod IV arm. One participant was randomized to the efgartigimod IV arm but did not receive efgartigimod because of an adverse event (AE) of Pyrexia.

Overall, 104 (94.5%) participants received all 4 efgartigimod doses. In the efgartigimod PH20 SC arm, 49 (89.1%) participants received all 4 doses. In the efgartigimod IV arm, 55 (100%) participants received all 4 doses.

A total of 178 participants rolled over to ARGX-113-2002 from ARGX-113-2001 and ARGX-113-1705. Of these, 53 participants received efgartigimod PH20 SC in ARGX-113-2001, 52 participants received efgartigimod IV in ARGX-113-2001, and 73 participants received efgartigimod IV in ARGX-113-1705. Of the 178 participants enrolled, 164 have received efgartigimod PH20 SC in the study and are defined as the total group. As of the data cutoff date, most participants (97.6%) were ongoing in the study. As of the data cutoff date, 2 participants with fatal serious AEs (SAEs) were recorded as ongoing.

The mean (SD) study duration was 169.7 (58.82) days. The mean (SD) duration of all cycles combined (excluding the period before the first administration of efgartigimod PH20 SC in ARGX-113-2002) was 160.6

(60.17) days, resulting in 72.1 patient-years of follow-up. As of the data cutoff date, the median cycle durations ranged from 50.0 to 56.0 days.

Pooling blocks

In support of the application for efgartigimod PH20 SC for the treatment of gMG, participant safety data were grouped into an SC PB and an IV PB:

- SC PB: The efgartigimod SC PB comprises data from all participants with gMG treated with efgartigimod coformulated with rHuPH20 for SC administration (efgartigimod PH20 SC) in ARGX-113-2001 and ARGX-113-2002 (through the safety data cutoff date of 02 Mar 2022).
- IV PB: The efgartigimod IV PB comprises data from participants with gMG treated with efgartigimod for IV administration (efgartigimod IV) in ARGX-113-1602, ARGX-113-1704, and ARGX-113-1705-IA4.

SC pooling block

An overview of cycle frequency and duration is presented in Table 26. The duration of treatment combined with follow-up in 6 months intervals is presented in Table 27.

Table 26: SC Pooling block: duration of Cycles (Safety analysis set)

	All cycles		Completed cycles	
Cycle X	N (%)	Individual cycle duration (days)[a] Median (min, max)	N (%)	Individual cycle duration (days)[a] Median (min, max)
1	168 (100)	70.5 (7, 246)	154 (91.7)	70.5 (42, 204)
2	149 (88.7)	52.0 (2, 106)	119 (70.8)	55.0 (48, 106)
3	117 (69.6)	50.0 (7, 129)	80 (47.6)	50.0 (49, 112)
4	80 (47.6)	50.0 (3, 86)	38 (22.6)	50.0 (50, 81)
5	38 (22.6)	28.0 (1, 52)	8 (4.8)	50.0 (48, 52)
6	8 (4.8)	11.5 (3, 45)	0	0

max=maximum; min=minimum; N=number of participants; X=number of cycles a The individual cycle duration is the median number of days from the first injection of a cycle to the first injection of the next cycle or the data cutoff date, whichever comes first; therefore, the duration of an individual participant's last cycle may appear shorter when considering all cycles

Table 27: SC pooling block: duration of treatment and follow-up combined (safety analysis set)

	Total (N=168)	
Treatment + follow-up duration	n (%)	Cn (C%)
6-Month intervals (months)		
6 to <12	104 (61.9)	104 (61.9)
<6	64 (38.1)	168 (100)

%=proportion of participants in each 6-month interval and the total number of participants; Cn=cumulative number of participants in each 6-month interval; C%=proportion of participants in each cumulative 6-month interval; N=number of participants in the analysis set; n=number of participants in each 6-month interval Note: 6-month intervals are: <6 months (<168 days); 6 to <12 months (168-350 days)

IV Pooling Block

An overview of duration of treatment is presented in Table 28.

Table 28: IV pooling block: duration of treatment combined with follow-up in 6-month intervals (safety analysis set)

	Total efgartigimod (N=164)	
Treatment + follow-up duration (months)	**n (%)**	**Cn (C%)**
30 to <36	21 (12.8)	21 (12.8)
24 to <30	42 (25.6)	63 (38.4)
18 to <24	42 (25.6)	105 (64.0)
12 to <18	20 (12.2)	125 (76.2)
6 to <12	18 (11.0)	143 (87.2)
<6	21 (12.8)	164 (100)

%=proportion of participants in each 6-month interval and the total number of participants; Cn=cumulative number of participants in each 6-month interval; C%=proportion of participants in each cumulative 6-month interval; N=number of participants in the analysis set; n=number of participants in each 6-month interval
Note: 6-month intervals are: <6 months (<168 days), 6 to <12 months (168-350 days), 12 to <18 months (351-532 days), 18 to <24 months (533-715 days), 24 to <30 months (716-897 days)

2.5.8.2. Adverse events

Studies ARGX-113-2001 and ARGX-113-2002

An overview of AEs in ARGX-113-2001 and ARGX-113-2002 is provided in table below.

Table 29: Studies ARGX-113-2001 and ARGX-113-2002: overview of adverse events (safety analysis set)

	Study ARGX-113-2001						Study ARGX-113-2002											
							Antecedent study treatment assignment											
	EFG SC (N=55)			EFG IV (N=55)			SC 2001 (N=51)			IV 2001 (N=48)			IV 1705 (N=65)			Total (N=164)		
	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU
Overall																		
≥1 AE	37 (67.3)	133	12.4	28 (50.9)	80	7.6	41 (80.4)	304	14.5	35 (72.9)	194	9.5	49 (75.4)	292	9.5	125 (76.2)	790	11.0
≥1 SAE	8 (14.5)	10	0.9	4 (7.3)	5	0.5	8 (15.7)	10	0.5	5 (10.4)	7	0.3	4 (6.2)	5	0.2	17 (10.4)	22	0.3
≥1 Grade 3 or higher AE	9 (16.4)	11	1.0	4 (7.3)	5	0.5	7 (13.7)	17	0.8	6 (12.5)	17	0.8	6 (9.2)	7	0.2	19 (11.6)	41	0.6
≥1 AE of special interest[a]	10 (18.2)	10	0.9	9 (16.4)	10	0.9	19 (37.3)	33	1.6	11 (22.9)	21	1.0	18 (27.7)	22	0.7	48 (29.3)	76	1.1
≥1 IRR[b]	14 (25.5)	20	1.9	2 (3.6)	2	0.2	20 (39.2)	76	3.6	16 (33.3)	47	2.3	24 (36.9)	116	3.8	60 (36.6)	239	3.3
≥1 ISR (localized)[c]	21 (38.2)	39	3.6	1 (1.8)	1	0.1	22 (43.1)	92	4.4	18 (37.5)	71	3.5	29 (44.6)	144	4.7	69 (42.1)	307	4.3
≥1 Fatal AE	0	…	…	0	…	…	0	…	…	1 (2.1)	1	0.0	1 (1.5)	2	0.1	2 (1.2)	3	0.0
≥1 Treatment-related AE according to PI	24 (43.6)	52	4.9	12 (21.8)	23	2.2	29 (56.9)	129	6.1	21 (43.8)	88	4.3	31 (47.7)	182	5.9	81 (49.4)	399	5.5
≥1 Procedure-related AE according to PI	14 (25.5)	22	2.1	2 (3.6)	2	0.2	12 (23.5)	44	2.1	8 (16.7)	36	1.8	11 (16.9)	64	2.1	31 (18.9)	144	2.0
≥1 Treatment-related SAE	0	…	…	0	…	…	1 (2.0)	1	0.0	0	…	…	0	…	…	1 (0.6)	1	0.0

	Study ARGX-113-2001						Study ARGX-113-2002											
							Antecedent study treatment assignment											
	EFG SC (N=55)			EFG IV (N=55)			SC 2001 (N=51)			IV 2001 (N=48)			IV 1705 (N=65)			Total (N=164)		
	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU	n (%)	m	PYFU
Overall																		
≥1 AE	37 (67.3)	133	12.4	28 (50.9)	80	7.6	41 (80.4)	304	14.5	35 (72.9)	194	9.5	49 (75.4)	292	9.5	125 (76.2)	790	11.0
≥1 SAE	8 (14.5)	10	0.9	4 (7.3)	5	0.5	8 (15.7)	10	0.5	5 (10.4)	7	0.3	4 (6.2)	5	0.2	17 (10.4)	22	0.3
≥1 Grade 3 or higher AE	9 (16.4)	11	1.0	4 (7.3)	5	0.5	7 (13.7)	17	0.8	6 (12.5)	17	0.8	6 (9.2)	7	0.2	19 (11.6)	41	0.6
≥1 AE of special interest[a]	10 (18.2)	10	0.9	9 (16.4)	10	0.9	19 (37.3)	33	1.6	11 (22.9)	21	1.0	18 (27.7)	22	0.7	48 (29.3)	76	1.1
≥1 IRR[b]	14 (25.5)	20	1.9	2 (3.6)	2	0.2	20 (39.2)	76	3.6	16 (33.3)	47	2.3	24 (36.9)	116	3.8	60 (36.6)	239	3.3
≥1 ISR (localized)[c]	21 (38.2)	39	3.6	1 (1.8)	1	0.1	22 (43.1)	92	4.4	18 (37.5)	71	3.5	29 (44.6)	144	4.7	69 (42.1)	307	4.3
≥1 Fatal AE	0	…	…	0	…	…	0	…	…	1 (2.1)	1	0.0	1 (1.5)	2	0.1	2 (1.2)	3	0.0
≥1 Treatment-related AE according to PI	24 (43.6)	52	4.9	12 (21.8)	23	2.2	29 (56.9)	129	6.1	21 (43.8)	88	4.3	31 (47.7)	182	5.9	81 (49.4)	399	5.5
≥1 Procedure-related AE according to PI	14 (25.5)	22	2.1	2 (3.6)	2	0.2	12 (23.5)	44	2.1	8 (16.7)	36	1.8	11 (16.9)	64	2.1	31 (18.9)	144	2.0
≥1 Treatment-related SAE	0	…	…	0	…	…	1 (2.0)	1	0.0	0	…	…	0	…	…	1 (0.6)	1	0.0

≥1 AE for which the study drug was interrupted	1 (1.8)	1	0.1	0	…	…	4 (7.8)	4	0.2	7 (14.6)	14	0.7	2 (3.1)	2	0.1	13 (7.9)	20	0.3
≥1 AE for which the study drug was discontinued	2 (3.6)	2	0.2	0	…	…	0	…	…	1 (2.1)	1	0.0	2 (3.1)	3	0.1	3 (1.8)	4	0.1

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; EFG=efgartigimod; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; IRR=infusion- or injection-related reaction; ISR=Injection site reaction; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PI=principal investigator; PYFU=person 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
Note: The SC 2001 group refers to participants who received efgartigimod PH20 in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002.
a An AESI was defined as any AE in the MedDRA SOC Infections and infestations.
B IRRs 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.
c Localized ISRs were defined as adverse events with MedDRA high level term Injection site reactions regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized Injection site reactions by high level term (refer to Section 2.1.5.2) and the SMQs for the injection- or infusion-related reactions. In study ARGX-113-2001, the AE of Injection site haematoma was incorrectly coded. It should have been coded as a Catheter site reaction. There were no AEs by PT of Injection site reactions in the efgartigimod IV arm

In study ARGX-113-2001, there were reported more AEs (67.3% vs. 50.9%), SAEs (14.5% vs 7.3%), Grade 3 or higher AEs (16.4% vs. 7.3%), Treatment related AEs (43.6% vs. 21.8%) and Procedure related AEs (25.5% vs. 3.6%) in the efgartigimod PH20 SC compared to the efgartigimod IV arm. The higher incidence of AEs, treatment- and procedure-related AEs in the efgartigimod PH20 SC arm compared with the efgartigimod IV arm is primarily due to Injection site reactions (38.2% vs. 1.8%).

AESIs were well balanced between the efgartigimod PH20 SC and IV arms (18.2% vs. 16.4%). No treatment related SAEs or fatal AEs were reported in both arms. 1 (1.8%) AE for which the study drug was interrupted and 2 (3.6%) AEs for which the study drug was discontinued were reported in the efgartigimod PH20 SC arm and none in the efgartigimod IV arm.

Analysis of the total group in ARGX-113-2002, which provides prolonged exposure to efgartigimod PH20 SC, show more reported AEs compared to the SC arm in study ARGX-113-2001 (76,2% vs. 67.3%). The higher frequency of injection site reactions contributes to this (42.2% vs. 38.2%). AESI were also higher in the total group in ARGX-113-2002 compared to the SC arm in study ARGX-113-2001 (29.3% vs. 18.2%), this will be assessed in the relevant section. To fatal cases were reported in the total group in study which will be assessed in the relevant section. No additional safety issues are observed with prolonged and repeated administration of efgartigimod PH20 SC.

SC Pooling Block

The overview of all AEs that occurred is presented in Table 30; those that occurred in C1 through C4 in Table 31; and those that occurred in the cohort of participants who started at least 4 cycles in Table 32.

Table 30: SC pooling block: overview of AEs (safety analysis set)

	AChR-Ab seropositive (N=137)		AChR-Ab seronegative (N=31)		Total (N=168)	
	n (%)	M	n (%)	m	n (%)	m
Overall						
≥1 AE	107 (78.1)	697	25 (80.6)	242	132 (78.6)	939
≥1 Serious adverse event	18 (13.1)	26	5 (16.1)	7	23 (13.7)	33
≥1 AE of CTCAE grade ≥3	21 (15.3)	41	5 (16.1)	12	26 (15.5)	53
≥1 Fatal AE	2 (1.5)	3	0 (0.0)	0	2 (1.2)	3
≥1 Treatment-related AE according to PI	66 (48.2)	306	21 (67.7)	147	87 (51.8)	453
≥1 Treatment-related SAE	1 (0.7)	1	0 (0.0)	0	1 (0.6)	1
≥1 AE leading to IMP interruption	13 (9.5)	20	1 (3.2)	1	14 (8.3)	21
≥1 AE leading to IMP discontinuation	5 (3.6)	6	0 (0.0)	0	5 (3.0)	6
≥1 AESI[a]	47 (34.3)	74	10 (32.3)	17	57 (33.9)	91
≥1 IRR[b]	49 (35.8)	182	16 (51.6)	77	65 (38.7)	259
≥1 ISR (localized)[c]	58 (42.3)	238	16 (51.6)	109	74 (44.0)	347

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Table 14.3.1.1.1.1

AChR-Ab=anti-acetylcholine receptor antibody; AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IRR=injection-related reaction; ISR=injection site reaction; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per AChR-Ab status; n=number of participants for whom the observation was reported; PI=principal investigator; SAE=serious adverse event; SC=subcutaneous; SMQ=standardized MedDRA queries; SOC=System Organ Class

[a] An AESI was defined as any AE in the MedDRA *Infections and infestations* SOC.

[d] IRRs 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.

[c] Localized ISRs were defined as AEs with the MedDRA high-level term *Injection site reaction* regardless of the time of AE onset relative to an injection. There is an overlap in the PTs for localized ISRs and the abovementioned SMQs for the injection- or infusion-related reactions.

Table 31: SC pooling block: overview of AEs by cycle through cycle 4 (safety analysis set)

	Total (N=168)											
	Cycle 1 (N=168)			Cycle 2 (N=149)			Cycle 3 (N=117)			Cycle 4 (N=80)		
	n (%)	m	95% CI[a]	n (%)	m	95% CI[a]	n (%)	m	95% CI[a]	n (%)	m	95% CI[a]
Overall												
≥1 AE	107 (63.7)	374	55.9-71.0	79 (53.0)	245	44.7-61.2	54 (46.2)	147	36.9-55.6	29 (36.3)	114	25.8-47.8
≥1 SAE	11 (6.5)	14	3.3-11.4	6 (4.0)	8	1.5-8.6	4 (3.4)	6	0.9-8.5	3 (3.8)	3	0.8-10.6
≥1 AE of CTCAE severity grade ≥3	13 (7.7)	18	4.2-12.9	9 (6.0)	19	2.8-11.2	5 (4.3)	7	1.4-9.7	3 (3.8)	3	0.8-10.6
≥1 Fatal AE	1 (0.6)	1	0.0-3.3	0	...	...	1 (0.9)	2	0.0-4.7	0	...	...
≥1 Treatment-related AE according to PI	70 (41.7)	192	34.1; 49.5	42 (28.2)	132	21.1-36.1	26 (22.2)	79	15.1-30.8	13 (16.3)	43	8.9-26.2
≥1 Treatment-related SAE	0	...	...	0	...	...	1 (0.9)	1	0.0-4.7	0	...	...
≥1 AE leading to interruption of IMP	6 (3.6)	6	1.3-7.6	7 (4.7)	13	1.9-9.4	2 (1.7)	2	0.2-6.0	0	...	...
≥1 AE leading to discontinuation of IMP	4 (2.4)	4	0.7-6.0	0	...	...	1 (0.9)	2	0.0-4.7	0	...	...
≥1 AESI[b]	21 (12.5)	24	7.9-18.5	23 (15.4)	29	10.0-22.3	18 (15.4)	21	9.4-23.2	9 (11.3)	10	5.3-20.3
≥1 Injection-related reaction[c]	45 (26.8)	87	20.3-34.2	35 (23.5)	79	16.9-31.1	17 (14.5)	54	8.7-22.2	10 (12.5)	35	6.2-21.8
≥1 Injection site reaction (localized)[d]	61 (36.3)	151	29.0-44.1	30 (20.1)	94	14.0-27.5	18 (15.4)	60	9.4-23.2	10 (12.5)	35	6.2-21.8

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per cycle; n=number of participants for whom the observation was reported; PI=principal investigator; PT=Preferred Term; SAE=serious adverse event; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class

a Clopper-Pearson 95% CI on the percentage of participants with events.

b An AESI was defined as any AE in the MedDRA SOC Infections and infestations.

c 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.

d Injection site reactions were defined as adverse events with MedDRA high level term Injection site reactions regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized Injection site reactions by high level term (refer to Section 2.1.5.2) and the SMQs for the injection- or infusion-related reactions.

Table 32: SC pooling block: overview of AEs in the cohort of participants who started at least 4 cycles of Efgartigimod PH20 SC by cycle and during all 4 cycles cumulatively (safety analysis set)

	Total (N=80)														
	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cumulative		
	n (%)	m	(95% CI)[a]	n (%)	m	(95% CI)[a]	n (%)	m	(95% CI)[a]	n (%)	m	(95% CI)[a]	n (%)	m	(95% CI)[a]
Overall															
≥1 AE	45 (56.3)	154	(44.7; 67.3)	39 (48.8)	120	(37.4; 60.2)	34 (42.5)	93	(31.5; 54.1)	29 (36.3)	114	(25.8; 47.8)	59 (73.8)	481	(62.7; 83.0)
≥1 SAE	6 (7.5)	8	(2.8; 15.6)	1 (1.3)	1	(0.0; 6.8)	0	...	...	3 (3.8)	3	(0.8; 10.6)	8 (10.0)	12	(4.4; 18.8)
≥1 AE of CTCAE severity grade ≥3	8 (10.0)	11	(4.4; 18.8)	3 (3.8)	4	(0.8; 10.6)	1 (1.3)	1	(0.0; 6.8)	3 (3.8)	3	(0.8; 10.6)	11 (13.8)	19	(7.1; 23.3)
≥1 Fatal AE	0	...	...	0	...	...	0	...	...	0	...	...	0	...	...
≥1 Treatment-related AE according to PI	31 (38.8)	68	(28.1; 50.3)	22 (27.5)	70	(18.1; 38.6)	17 (21.3)	46	(12.9; 31.8)	13 (16.3)	43	(8.9; 26.2)	43 (53.8)	227	(42.2; 65.0)
≥1 Treatment-related SAE	0	...	...	0	...	...	0	...	...	0	...	...	0	...	...
≥1 AE leading to interruption of IMP	3 (3.8)	3	(0.8; 10.6)	0	...	...	1 (1.3)	1	(0.0; 6.8)	0	...	...	4 (5.0)	4	(1.4; 12.3)
≥1 AE leading to discontinuation of IMP	1 (1.3)	1	(0.0; 6.8)	0	...	...	0	...	...	0	...	...	1 (1.3)	1	(0.0; 6.8)
≥1 AESI[b]	10 (12.5)	11	(6.2; 21.8)	10 (12.5)	12	(6.2; 21.8)	14 (17.5)	17	(9.9; 27.6)	9 (11.3)	10	(5.3; 20.3)	30 (37.5)	50	(26.9; 49.0)
≥1 Injection-related reaction[c]	15 (18.8)	29	(10.9; 29.0)	14 (17.5)	41	(9.9; 27.6)	11 (13.8)	31	(7.1; 23.3)	10 (12.5)	35	(6.2; 21.8)	25 (31.3)	136	(21.3; 42.6)
≥1 Injection site reaction (localized)[d]	24 (30.0)	53	(20.3; 41.3)	14 (17.5)	52	(9.9; 27.6)	12 (15.0)	35	(8.0; 24.7)	10 (12.5)	35	(6.2; 21.8)	32 (40.0)	175	(29.2; 51.6)

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PI=principal investigator; PT=Preferred Term; SAE=serious adverse event; SC=subcutaneous(ly); SMQ=standardized MedDRA query; SOC=System Organ Class
a Clopper-Pearson 95% CI on the percentage of participants with events
b An AESI was defined as any AE in the MedDRA SOC Infections and infestations.
c 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.
d Injection site reactions were defined as adverse events with MedDRA high level term Injection site reactions regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized Injection site reactions by high level term (refer to Section 2.1.5.2) and the SMQs for the injection- or infusion-related reactions.

In the total group (N=168), 132 (78.6%) participants had ≥1 AE, 23 (13.7%) had 14 ≥1 SAE, 26 (15.5%) had AEs with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3, 14 (8.3%) had AEs that resulted in interruption and 5 (3.0%) had AEs that resulted in discontinuation. Adverse events of special interest (AESIs) occurred in 57 (33.9%) participants in the total group. These frequencies are similar to the observations in study ARGX-113-2002.

One (0.6%) participant in the total group had a treatment-related SAE. Fatal AEs occurred in 2 (1.2%) participants in the total group.

The frequency of participants with ≥1 AE in the total group decreased with each subsequent cycle and with each subsequent cycle of efgartigimod PH20 SC the incidence of AESIs did not seem to increase.

IV Pooling Block

The overview of all AEs that occurred is presented in Table 33 (all cycles combined); those that occurred in cycles 1 through 10 in Table 34; and those that occurred in the cohort of participants who started at least 8 cycles in Table 35.

Table 33: IV pooling block: overview of AEs reported (safety analysis set)

	Total efgartigimod (N=164)		
	n (%)	m	100 PYFU
Overall			
≥1 AE	143 (87.2)	1109	416.9
≥1 SAE	38 (23.2)	56	21.0
≥1 AE of CTCAE grade ≥3	43 (26.2)	82	30.8
≥1 Fatal AE	5 (3.0)	5	1.9
≥1 Treatment-related AE according to PI[a]	66 (40.2)	262	98.5
≥1 Treatment-related SAE[a]	2 (1.2)	2	0.8
≥1 AE leading to interruption of IMP	24 (14.6)	37	13.9
≥1 AE leading to discontinuation of IMP	15 (9.1)	21	7.9
≥1 AESI[b]	101 (61.6)	229	86.1
≥1 Infusion-related reaction[c]	18 (11.0)	25	9.4

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PI=principal investigator; 100 PYFU=event rates per 100 person years of follow-up calculated as 100 * number of events/sum of follow-up time of all participants expressed in years in the applicable period; SAE=serious adverse event; SMQ=standardized MedDRA query

a Treatment-related was defined as at least possibly related to IMP according to the PI, or a missing drug relatedness.

b An AESI was defined as any AE in the MedDRA SOC Infections and infestations.

c Infusion-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

Table 34: IV Pooling Block: Overview of AEs by Cycle Through Cycle 10 (Safety Analysis Set)

	Total efgartigimod (N=164)																			
	Cycle 1 (N=164)		Cycle 2 (N=144)		Cycle 3 (N=128)		Cycle 4 (N=116)		Cycle 5 (N=105)		Cycle 6 (N=98)		Cycle 7 (N=84)		Cycle 8 (N=79)		Cycle 9 (N=70)		Cycle 10 (N=64)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall																				
≥1 AE	109 (66.5)	339	72 (50.0)	159	54 (42.2)	151	53 (45.7)	110	32 (30.5)	62	31 (31.6)	54	26 (31.0)	38	26 (32.9)	47	21 (30.0)	36	21 (32.8)	33
≥1 SAE	3 (1.8)	3	8 (5.6)	9	6 (4.7)	10	8 (6.9)	8	1 (1.0)	1	4 (4.1)	8	2 (2.4)	2	4 (5.1)	4	3 (4.3)	4	1 (1.6)	2
≥1 AE of CTCAE severity grade ≥3	8 (4.9)	9	10 (6.9)	13	8 (6.3)	19	11 (9.5)	11	3 (2.9)	3	5 (5.1)	10	1 (1.2)	1	4 (5.1)	4	3 (4.3)	4	2 (3.1)	2
≥1 Fatal AE	0	...	0	...	2 (1.6)	2	2 (1.7)	2	0	...	1 (1.0)	1	0	...	0	...	0	...	0	...
≥1 Treatment-related AE according to PI[a]	45 (27.4)	110	16 (11.1)	28	14 (10.9)	29	16 (13.8)	28	9 (8.6)	17	11 (11.2)	14	3 (3.6)	7	5 (6.3)	6	4 (5.7)	8	4 (6.3)	7
≥1 Treatment-related SAE[a]	1 (0.6)	1	0	...	0	...	0	...	0	...	0	...	1 (1.2)	1	0	...	0	...	0	...
≥1 AE leading to interruption of IMP	4 (2.4)	5	2 (1.4)	4	7 (5.5)	8	4 (3.4)	7	1 (1.0)	1	2 (2.0)	3	2 (2.4)	2	0	...	3 (4.3)	3	0	...
≥1 AE leading to discontinuation of IMP	2 (1.2)	6	1 (0.7)	1	2 (1.6)	2	3 (2.6)	4	1 (1.0)	1	3 (3.1)	4	0	...	2 (2.5)	2	0	...	0	...
≥1 AESI[b]	50 (30.5)	61	32 (22.2)	41	25 (19.5)	32	19 (16.4)	28	8 (7.6)	8	8 (8.2)	13	9 (10.7)	9	4 (5.1)	4	6 (8.6)	7	8 (12.5)	10
≥1 Infusion-related reaction[c]	3 (1.8)	3	4 (2.8)	4	2 (1.6)	2	3 (2.6)	3	3 (2.9)	3	2 (2.0)	2	1 (1.2)	2	0	...	2 (2.9)	2	2 (3.1)	2

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per cycle; n=number of participants for whom the observation was reported; PI=principal investigator; SAE=serious adverse event; SMQ=standardized MedDRA query; SOC=System Organ Class

a Treatment-related was defined as at least possibly related to IMP according to the PI, or a missing drug relatedness.

b An AESI was defined as any AE in the MedDRA SOC Infections and infestations.

c Infusion-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.

Table 35: IV Pooling Block: Overview of AEs in the Cohort of Participants Who Started At Least 8 Cycles of Efgartigimod by Cycle and During All 8 Cycles Cumulatively (Safety Analysis Set)

	Total efgartigimod (N=79)																	
	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cumulative	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AE	54 (68.4)	136	37 (46.8)	75	29 (36.7)	81	33 (41.8)	57	25 (31.6)	52	25 (31.6)	38	24 (30.4)	35	26 (32.9)	47	72 (91.1)	521
≥1 SAE	0	...	2 (2.5)	2	1 (1.3)	1	1 (1.3)	1	0	...	1 (1.3)	1	1 (1.3)	1	4 (5.1)	4	10 (12.7)	10
≥1 AE of CTCAE severity grade ≥3	2 (2.5)	3	3 (3.8)	3	3 (3.8)	3	4 (5.1)	4	2 (2.5)	2	2 (2.5)	2	1 (1.3)	1	4 (5.1)	4	15 (19.0)	22
≥1 Fatal AE	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...
≥1 Treatment-related AE according to PI AE[a]	23 (29.1)	56	9 (11.4)	12	9 (11.4)	21	12 (15.2)	18	9 (11.4)	17	9 (11.4)	12	2 (2.5)	5	5 (6.3)	6	36 (45.6)	147
≥1 Treatment-related SAE[a]	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...
≥1 AE leading to interruption of IMP	2 (2.5)	2	1 (1.3)	2	2 (2.5)	2	3 (3.8)	3	1 (1.3)	1	2 (2.5)	3	2 (2.5)	2	0	...	12 (15.2)	15
≥1 AE leading to discontinuation of IMP	0	...	0	...	0	...	0	...	0	...	0	...	0	...	2 (2.5)	2	2 (2.5)	2
≥1 AESI[b]	22 (27.8)	26	18 (22.8)	25	12 (15.2)	14	11 (13.9)	11	5 (6.3)	5	5 (6.3)	6	8 (10.1)	8	4 (5.1)	4	48 (60.8)	99
≥1 Infusion-related reaction[c]	1 (1.3)	1	3 (3.8)	3	2 (2.5)	2	3 (3.8)	3	2 (2.5)	2	2 (2.5)	2	0	...	0	...	9 (11.4)	13

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per cycle; n=number of participants for whom the observation was reported; PI=principal investigator; SAE=serious adverse event; SMQ=standardized MedDRA query; SOC=System Organ Class
a Treatment-related was defined as at least possibly related to IMP according to the PI, or a missing drug relatedness.
b An AESI was defined as any AE in the MedDRA SOC Infections and infestations.
c Infusion-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.

Of the 164 participants, 143 (87.2%) had ≥1 AE in up to 19 cycles of treatment, 38 (23.2%) had SAEs, 43 (26.2%) had AEs with CTCAE grade ≥3, 24 (14.6%) participants had AEs that resulted in interruption and 15 (9.1%) participants had AEs that resulted in discontinuation.

Treatment-related SAEs occurred in 2 participants. 5 (3.0%) participants had fatal AEs. None of the fatal AEs were considered by the investigator to be related to efgartigimod.

The frequency of participants with ≥1 AEs or AESIs observed in the total efgartigimod group decreased with each subsequent cycle up to C5 and then remained stable.

Common Adverse Events

Studies ARGX-113-2001 and ARGX-113-2002

Common adverse events for study ARGX-113-2001 are presented in table below.

Table 36: Common (≥ 2 participants in either arm) AEs by MedDRA SOC and PT (safety analysis set)

	EFG PH20 SC (N=55)		EFG IV (N=55)		Total (N=110)	
	n (%)	m	n (%)	m	n (%)	m
≥1 AE	37 (67.3)	133	28 (50.9)	80	65 (59.1)	213
Gastrointestinal disorders	8 (14.5)	17	6 (10.9)	10	14 (12.7)	27
Abdominal discomfort	2 (3.6)	2	0	…	2 (1.8)	2
Abdominal pain upper	2 (3.6)	3	0	…	2 (1.8)	3
Diarrhoea	1 (1.8)	5	3 (5.5)	3	4 (3.6)	8
Nausea	0	…	2 (3.6)	2	2 (1.8)	2
General disorders and administration site conditions	25 (45.5)	50	6 (10.9)	8	31 (28.2)	58
Fatigue	2 (3.6)	2	3 (5.5)	3	5 (4.5)	5
Injection site bruising	4 (7.3)	4	0	…	4 (3.6)	4
Injection site erythema	7 (12.7)	7	0	…	7 (6.4)	7
Injection site pain	3 (5.5)	3	0	…	3 (2.7)	3
Injection site pruritus	5 (9.1)	5	0	…	5 (4.5)	5
Injection site rash	8 (14.5)	14	0	…	8 (7.3)	14
Injection site urticaria	2 (3.6)	2	0	…	2 (1.8)	2
Pyrexia	2 (3.6)	2	0	…	2 (1.8)	2

Infections and infestations	10 (18.2)	10	9 (16.4)	10	19 (17.3)	20
COVID-19	2 (3.6)	2	0	…	2 (1.8)	2
Pharyngitis	2 (3.6)	2	0	…	2 (1.8)	2
Urinary tract infection	1 (1.8)	1	3 (5.5)	3	4 (3.6)	4
Injury, poisoning and procedural complications	3 (5.5)	6	7 (12.7)	11	10 (9.1)	17
Contusion	0	…	3 (5.5)	3	3 (2.7)	3
Fall	1 (1.8)	1	3 (5.5)	3	4 (3.6)	4
Metabolism and nutrition disorders	2 (3.6)	2	0	…	2 (1.8)	2
Hypokalaemia	2 (3.6)	2	0	…	2 (1.8)	2
Musculoskeletal and connective tissue disorders	5 (9.1)	5	2 (3.6)	2	7 (6.4)	7
Pain in extremity	2 (3.6)	2	0	…	2 (1.8)	2
Nervous system disorders	15 (27.3)	23	9 (16.4)	16	24 (21.8)	39
Headache	7 (12.7)	10	7 (12.7)	11	14 (12.7)	21
Migraine	2 (3.6)	2	0	…	2 (1.8)	2
Myasthenia gravis	6 (10.9)	8	1 (1.8)	2	7 (6.4)	10
Syncope	2 (3.6)	2	0	…	2 (1.8)	2
Vascular disorders	2 (3.6)	2	2 (3.6)	2	4 (3.6)	4
Hypertension	2 (3.6)	2	1 (1.8)	1	3 (2.7)	3

Source: Table 14.3.1.2
AE=adverse event; EFG=efgartigimod; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants per arm in the analysis set, which was the denominator for the percentages; n=number of participants with at least 1 event; PT=Preferred Term; SC=subcutaneous(ly); SOC=System Organ Class
Notes: AEs were coded by SOC and PT according to MedDRA Version 24.1 (Sep 2021). Participants with multiple events within the same SOC or PT were only counted once under those categories.

Common AEs for study ARGX-113-2001 and ARGX-113-2002 are presented below.

Table 37: Studies ARGX-113-2001 and ARGX-113-2002: Common (≥5% of Participants in the Total Group in Study ARGX-113-2002) AEs, by SOC and PT (Safety Analysis Set)

System organ class / Preferred term	Study ARGX-113-2001				Study ARGX-113-2002							
					Antecedent study treatment assignment						Total (N=164)	
	EFG SC (N=55)		EFG IV (N=55)		SC 2001 (N=51)		IV 2001 (N=48)		IV 1705 (N=65)			
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AE	37 (67.3)	133	28 (50.9)	80	41 (80.4)	304	35 (72.9)	194	49 (75.4)	292	125 (76.2)	790
General disorders and administration site conditions	25 (45.5)	50	6 (10.9)	8	24 (47.1)	99	23 (47.9)	85	30 (46.2)	149	77 (47.0)	333
Injection site erythema	7 (12.7)	7	0	...	11 (21.6)	41	12 (25.0)	32	19 (29.2)	77	42 (25.6)	150
Injection site pain	3 (5.5)	3	0	...	4 (7.8)	7	3 (6.3)	7	8 (12.3)	14	15 (9.1)	28
Injection site pruritus	5 (9.1)	5	0	...	5 (9.8)	7	3 (6.3)	8	7 (10.8)	15	15 (9.1)	30
Injection site bruising	4 (7.3)	4	0	...	5 (9.8)	7	2 (4.2)	2	6 (9.2)	9	13 (7.9)	18
Injection site rash	8 (14.5)	14	0	...	4 (7.8)	7	5 (10.4)	7	2 (3.1)	3	11 (6.7)	17
Injection site swelling	0	...	0	...	2 (3.9)	4	1 (2.1)	5	6 (9.2)	12	9 (5.5)	21
Infections and infestations	10 (18.2)	10	9 (16.4)	10	19 (37.3)	33	11 (22.9)	21	18 (27.7)	22	48 (29.3)	76
COVID-19	2 (3.6)	2	0	...	7 (13.7)	7	4 (8.3)	5	8 (12.3)	8	19 (11.6)	20
Nasopharyngitis	0	...	0	...	3 (5.9)	3	2 (4.2)	4	5 (7.7)	5	10 (6.1)	12
Nervous system disorders	15 (27.3)	23	9 (16.4)	16	20 (39.2)	47	5 (10.4)	6	14 (21.5)	32	39 (23.8)	85
Headache	7 (12.7)	10	7 (12.7)	11	12 (23.5)	32	2 (4.2)	3	11 (16.9)	23	25 (15.2)	58
Gastrointestinal disorders	8 (14.5)	17	6 (10.9)	10	10 (19.6)	17	8 (16.7)	18	11 (16.9)	16	29 (17.7)	51
Diarrhoea	1 (1.8)	5	3 (5.5)	3	5 (9.8)	9	4 (8.3)	7	3 (4.6)	4	12 (7.3)	20

AE=adverse event; m=number of events; CSR=clinical study report; EFG=efgartigimod; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IV=intravenous(ly); MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class
Notes: Adverse events were coded by SOC and PT using MedDRA version 24.1 (Sep 2021).
The SC 2001 group refers to participants who received efgartigimod PH20 in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002

In study ARGX-113-2001, the most common reported AEs were Injection site rash (8 [14.5%] participants in the SC arm vs. 0 in the IV arm), Headache (7 [12.7%] participants each in both arms), Injection site erythema (7 [12.7%] participants in the SC arm and 0 in the IV arm), myasthenia gravis (6 [10.9%] participants in the SC arm and 1 [1.8%] in the IV arm).

In ARGX-113-2002, the most commonly reported AEs in were Injection site erythema, Headache, COVID-19, Injection site pain, Injection site pruritus, Injection site bruising, Diarrhea, Injection site rash, Nasopharyngitis, and Injection site swelling.

SC Pooling Block

Common AEs that occurred in ≥5% participants in the total group are presented by SOC and PT in Table 38. PTs that occurred in ≥2% of participants during any cycle through C4 are presented in Table 39.

Table 38: 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	AChR-Ab seropositive (N=137)		AChR-Ab seronegative (N=31)		Total (N=168)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse event	107 (78.1)	697	25 (80.6)	242	132 (78.6)	939
General disorders and administration site conditions	70 (51.1)	263	16 (51.6)	121	86 (51.2)	384
Injection site erythema	34 (24.8)	113	11 (35.5)	44	45 (26.8)	157
Injection site pruritus	12 (8.8)	22	5 (16.1)	13	17 (10.1)	35
Injection site rash	13 (9.5)	24	3 (9.7)	7	16 (9.5)	31
Injection site pain	10 (7.3)	21	5 (16.1)	10	15 (8.9)	31
Injection site bruising	9 (6.6)	12	5 (16.1)	10	14 (8.3)	22
Injection site swelling	4 (2.9)	10	5 (16.1)	11	9 (5.4)	21
Infections and infestations	47 (34.3)	74	10 (32.3)	17	57 (33.9)	91
COVID-19	17 (12.4)	18	4 (12.9)	4	21 (12.5)	22
Nasopharyngitis	9 (6.6)	11	2 (6.5)	2	11 (6.5)	13
Nervous system disorders	37 (27.0)	93	9 (29.0)	16	46 (27.4)	109
Headache	25 (18.2)	60	4 (12.9)	8	29 (17.3)	68
Myasthenia gravis	9 (6.6)	16	3 (9.7)	3	12 (7.1)	19
Gastrointestinal disorders	24 (17.5)	46	12 (38.7)	23	36 (21.4)	69
Diarrhoea	6 (4.4)	16	6 (19.4)	9	12 (7.1)	25

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Table 14.3.1.1.2.1
AChR-Ab=anti-acetylcholine receptor antibody; AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per AChR-Ab status; n=number of participants for whom the observation was reported; PT=Preferred Term; SC=subcutaneous; SOC=System Organ Class
Note: Adverse events were coded by SOC and PT using MedDRA version 24.1 (September 2021).

Table 39: SC Pooling Block: AEs That Occurred in ≥2% of Participants During Any Cycle Through Cycle 4 by Cycle, SOC, and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)							
	Cycle 1 (N=168)		Cycle 2 (N=149)		Cycle 3 (N=117)		Cycle 4 (N=80)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AE	107 (63.7)	374	79 (53.0)	245	54 (46.2)	147	29 (36.3)	114
General disorders and administration site conditions	68 (40.5)	173	39 (26.2)	105	18 (15.4)	61	10 (12.5)	36
Injection site erythema	32 (19.0)	54	19 (12.8)	40	13 (11.1)	34	9 (11.3)	25
Injection site rash	15 (8.9)	24	4 (2.7)	5	2 (1.7)	2	0	...
Injection site pruritus	14 (8.3)	18	9 (6.0)	17	0	...	0	...
Injection site pain	11 (6.5)	16	6 (4.0)	10	2 (1.7)	4	1 (1.3)	1
Injection site bruising	10 (6.0)	10	3 (2.0)	5	3 (2.6)	6	0	...
Injection site swelling	6 (3.6)	6	3 (2.0)	5	2 (1.7)	7	2 (2.5)	3
Fatigue	5 (3.0)	5	2 (1.3)	2	0	...	0	...
Injection site oedema	3 (1.8)	4	3 (2.0)	8	1 (0.9)	2	2 (2.5)	4
Pyrexia	3 (1.8)	3	3 (2.0)	3	0	...	0	...
Nervous system disorders	31 (18.5)	46	17 (11.4)	20	6 (5.1)	10	10 (12.5)	18
Headache	20 (11.9)	25	9 (6.0)	10	5 (4.3)	7	6 (7.5)	13
Myasthenia gravis	8 (4.8)	13	2 (1.3)	2	1 (0.9)	2	2 (2.5)	2
Infections and infestations	21 (12.5)	24	23 (15.4)	29	18 (15.4)	21	9 (11.3)	10
COVID-19	4 (2.4)	4	9 (6.0)	10	5 (4.3)	5	1 (1.3)	1
Nasopharyngitis	3 (1.8)	3	4 (2.7)	4	2 (1.7)	3	2 (2.5)	2
Gastrointestinal disorders	19 (11.3)	31	14 (9.4)	20	9 (7.7)	14	3 (3.8)	4
Diarrhoea	4 (2.4)	9	7 (4.7)	10	3 (2.6)	6	0	...
Nausea	3 (1.8)	3	3 (2.0)	3	3 (2.6)	3	0	...
Musculoskeletal and connective tissue disorders	13 (7.7)	14	9 (6.0)	15	7 (6.0)	10	7 (8.8)	11
Muscle spasms	3 (1.8)	3	3 (2.0)	3	1 (0.9)	1	0	...
Arthralgia	2 (1.2)	2	2 (1.3)	3	1 (0.9)	1	2 (2.5)	2
Back pain	2 (1.2)	2	2 (1.3)	2	3 (2.6)	4	1 (1.3)	1
Neck pain	1 (0.6)	1	0	...	1 (0.9)	1	2 (2.5)	2
Respiratory, thoracic and mediastinal disorders	8 (4.8)	11	6 (4.0)	8	3 (2.6)	5	6 (7.5)	8
Cough	1 (0.6)	1	1 (0.7)	1	0	...	2 (2.5)	2
Skin and subcutaneous tissue disorders	6 (3.6)	7	8 (5.4)	11	3 (2.6)	6	2 (2.5)	3
Pruritus	1 (0.6)	1	4 (2.7)	4	1 (0.9)	1	0	...
Blood and lymphatic system disorders	3 (1.8)	3	4 (2.7)	4	2 (1.7)	2	0	...
Anaemia	1 (0.6)	1	4 (2.7)	4	2 (1.7)	2	0	...

AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per cycle; n=number of participants for whom the observation was reported; PT=Preferred Term; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021).

The most commonly reported AEs were Injection site erythema (26.8%), Headache (17.3%), COVID-19 (12.5%), and Injection site pruritus (10.1%). The frequencies were similar to study ARGX-113-2001 and ARGX-113-2002.

Overall, the frequency of AEs decreased with each subsequent cycle and the 3-month interval data showed a decrease in the frequency of participants with AEs.

IV Pooling Block

A summary of common AEs that occurred in ≥5 participants in the total efgartigimod group is presented by SOC and PT in table below.

Table 40: 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	AChR-Ab seropositive (N=127)		AChR-Ab seronegative (N=37)		Total (N=164)	
	n (%)	m	n (%)	m	n (%)	m
Any adverse event	108 (85.0)	822	35 (94.6)	287	143 (87.2)	1109
Infections and infestations	76 (59.8)	177	25 (67.6)	52	101 (61.6)	229
Nasopharyngitis	22 (17.3)	30	6 (16.2)	7	28 (17.1)	37
Urinary tract infection	13 (10.2)	17	6 (16.2)	10	19 (11.6)	27
COVID-19	14 (11.0)	14	4 (10.8)	4	18 (11.0)	18
Upper respiratory tract infection	12 (9.4)	17	1 (2.7)	1	13 (7.9)	18
Nervous system disorders	59 (46.5)	185	21 (56.8)	56	80 (48.8)	241
Headache	43 (33.9)	116	16 (43.2)	33	59 (36.0)	149
Myasthenia gravis	9 (7.1)	10	2 (5.4)	3	11 (6.7)	13
Dizziness	7 (5.5)	11	3 (8.1)	3	10 (6.1)	14
Gastrointestinal disorders	37 (29.1)	80	13 (35.1)	23	50 (30.5)	103
Diarrhoea	17 (13.4)	23	3 (8.1)	3	20 (12.2)	26
Nausea	12 (9.4)	17	4 (10.8)	4	16 (9.8)	21
Vomiting	6 (4.7)	10	3 (8.1)	3	9 (5.5)	13

Musculoskeletal and connective tissue disorders	31 (24.4)	53	15 (40.5)	25	46 (28.0)	78
Arthralgia	8 (6.3)	11	6 (16.2)	7	14 (8.5)	18
Back pain	10 (7.9)	10	1 (2.7)	1	11 (6.7)	11
Myalgia	10 (7.9)	14	0 (0.0)	0	10 (6.1)	14
General disorders and administration site conditions	28 (22.0)	47	13 (35.1)	17	41 (25.0)	64
Pyrexia	9 (7.1)	9	3 (8.1)	3	12 (7.3)	12
Respiratory, thoracic and mediastinal disorders	21 (16.5)	27	8 (21.6)	12	29 (17.7)	39
Oropharyngeal pain	9 (7.1)	9	3 (8.1)	3	12 (7.3)	12
Vascular disorders	14 (11.0)	22	6 (16.2)	9	20 (12.2)	31
Hypertension	8 (6.3)	12	2 (5.4)	4	10 (6.1)	16

Source: Module 5.3.5.3, ARGX-113-9021-9031-ISS, Table 14.3.1.2.2.1
AChR-Ab=anti-acetylcholine receptor antibody; AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per AChR-Ab status; n=number of participants for whom the observation was reported; PT=Preferred Term; SOC=System Organ Class
Note: Adverse events were coded by SOC and PT using MedDRA version 24.1 (September 2021).

PTs that occurred in ≥3 participants in the total efgartigimod group during any cycle through C10 are presented below.

Table 41: IV Pooling Block: AEs That Occurred in ≥3 Participants in the Total Efgartigimod Group During Any Cycle Through Cycle 10 by Cycle, SOC, and PT (Safety Analysis Set)

	Total efgartigimod																			
	Cycle 1 (N=164)		Cycle 2 (N=144)		Cycle 3 (N=128)		Cycle 4 (N=116)		Cycle 5 (N=105)		Cycle 6 (N=98)		Cycle 7 (N=84)		Cycle 8 (N=79)		Cycle 9 (N=70)		Cycle 10 (N=64)	
System organ class[a]																				
Preferred term	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
≥1 AE	109 (66.5)	339	72 (50.0)	159	54 (42.2)	151	53 (45.7)	110	32 (30.5)	62	31 (31.6)	54	26 (31.0)	38	26 (32.9)	47	21 (30.0)	36	21 (32.8)	33
Infections and infestations	50 (30.5)	61	32 (22.2)	41	25 (19.5)	32	19 (16.4)	28	8 (7.6)	8	8 (8.2)	13	9 (10.7)	9	4 (5.1)	4	6 (8.6)	7	8 (12.5)	10
Nasopharyngitis	12 (7.3)	12	9 (6.3)	9	5 (3.9)	6	4 (3.4)	4	0	...	0	...	2 (2.4)	2	1 (1.3)	1	1 (1.4)	1	2 (3.1)	2
Upper respiratory tract infection	10 (6.1)	10	4 (2.8)	5	1 (0.8)	1	1 (0.9)	1	1 (1.0)	1	0	...	0	...	0	...	0	...	0	...
Urinary tract infection	9 (5.5)	10	1 (0.7)	1	6 (4.7)	6	3 (2.6)	4	2 (1.9)	2	1 (1.0)	1	0	...	1 (1.3)	1	0	...	1 (1.6)	1
Bronchitis	4 (2.4)	5	2 (1.4)	2	0	...	0	...	0	...	0	...	2 (2.4)	2	0	...	0	...	2 (3.1)	2
Influenza	3 (1.8)	3	1 (0.7)	1	0	...	1 (0.9)	1	0	...	0	...	0	...	0	...	0	...	0	...
COVID-19	1 (0.6)	1	1 (0.7)	1	0	...	4 (3.4)	4	0	...	1 (1.0)	1	2 (2.4)	2	0	...	2 (2.9)	2	2 (3.1)	2
Herpes zoster	1 (0.6)	1	3 (2.1)	3	0	...	1 (0.9)	1	0	...	1 (1.0)	1	0		1 (1.3)	1	0	...	0	...
Nervous system disorders	43 (26.2)	87	22 (15.3)	32	20 (15.6)	34	15 (12.9)	20	11 (10.5)	16	6 (6.1)	8	6 (7.1)	6	6 (7.6)	11	3 (4.3)	9	3 (4.7)	6
Headache	34 (20.7)	60	14 (9.7)	18	11 (8.6)	18	11 (9.5)	15	4 (3.8)	4	2 (2.0)	3	3 (3.6)	3	3 (3.8)	8	2 (2.9)	6	2 (3.1)	5
Dizziness	4 (2.4)	7	1 (0.7)	1	1 (0.8)	1	0	...	2 (1.9)	3	0	...	1 (1.2)	1	0	...	0	...	0	...
Paraesthesia	3 (1.8)	3	1 (0.7)	1	0	...	0	...	0	...	0	...	1 (1.2)	1	0	...	0	...	0	...
Hypoaesthesia	1 (0.6)	1	3 (2.1)	3	1 (0.8)	1	0	...	0	...	0	...	0	...	0	...	0	...	0	...

Gastrointestinal disorders	26 (15.9)	31	9 (6.3)	15	13 (10.2)	18	9 (7.8)	15	6 (5.7)	7	3 (3.1)	4	1 (1.2)	1	4 (5.1)	4	1 (1.4)	1	1 (1.6)	1
Diarrhoea	8 (4.9)	8	5 (3.5)	6	2 (1.6)	2	3 (2.6)	4	3 (2.9)	3	1 (1.0)	1	0	...	1 (1.3)	1	0	...	0	...
Nausea	7 (4.3)	7	3 (2.1)	3	5 (3.9)	5	0	...	3 (2.9)	3	1 (1.0)	1	0	...	0	...	0	...	0	...
Vomiting	3 (1.8)	4	2 (1.4)	3	1 (0.8)	2	3 (2.6)	3	0		0	...	0	...	0	...	0	...	0	...
Musculoskeletal and connective tissue disorders	19 (11.6)	26	8 (5.6)	9	2 (1.6)	2	10 (8.6)	12	3 (2.9)	3	4 (4.1)	4	1 (1.2)	1	4 (5.1)	7	3 (4.3)	3	2 (3.1)	2
Myalgia	6 (3.7)	8	1 (0.7)	1	1 (0.8)	1	2 (1.7)	3	1 (1.0)	1	0	...	0	...	0	...	0	...	0	...
Arthralgia	4 (2.4)	4	1 (0.7)	1	0	...	3 (2.6)	3	0	...	2 (2.0)	2	0	...	2 (2.5)	2	1 (1.4)	1	2 (3.1)	2
Pain in extremity	4 (2.4)	5	0		0	...	0	...	1 (1.0)	1	0	...	0	...	1 (1.3)	1	0	...	0	...
Back pain	2 (1.2)	2	3 (2.1)	3	0	...	1 (0.9)	1	1 (1.0)	1	1 (1.0)	1	1 (1.2)	1	0		2 (2.9)	2	0	...
Injury, poisoning and procedural complications	14 (8.5)	20	3 (2.1)	7	5 (3.9)	5	3 (2.6)	3	3 (2.9)	3	3 (3.1)	3	2 (2.4)	3	2 (2.5)	3	3 (4.3)	4	3 (4.7)	3
Contusion	5 (3.0)	5	1 (0.7)	1	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...
Procedural headache	4 (2.4)	4	0	...	1 (0.8)	1	1 (0.9)	1	0	...	0	...	0	...	0	...	0	...	0	...
Fall	3 (1.8)	3	0	...	0	...	0	...	1 (1.0)	1	0	...	0	...	0	...	0	...	1 (1.6)	1
Skin abrasion	3 (1.8)	3	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...	0	...

AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per cycle; n=number of participants for whom the observation was reported; PT=Preferred Term; SOC=System Organ Class;
Note: AEs were coded using MedDRA version 24.1 (Sep 2021).
a Each SOC presented in the table includes the number of participants for whom the observation was reported and the number of events for the entire category and not only the PTs that met the cutoff for inclusion in the table

The most commonly reported AEs were Headache (36.0%), Nasopharyngitis (17.1%), Diarrhoea (12.2%), Urinary tract infection (11.6%), and COVID-19 (11.0%).

AEs of Myasthenia gravis occurred in 11 (6.7%) participants in the total group.

A higher number of cycles per participant does not appear to be associated with a higher frequency of AEs.

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

Two fatal cases were reported in participants with gMG who received efgartigimod PH20 SC; both events occurred during ARGX-113-2002:

- One participant with a history of renal cancer with no evidence of reoccurrence for >3 years at screening died because of an SAE of Renal cancer metastatic:

The participant was diagnosed with myasthenia gravis in 2017. Other medical history included renal cell carcinoma. At the time of the SAE of renal cancer metastatic in study ARGX-113-2002, the participant had received 4 doses and completed 1 period of efgartigimod PH20 SC 1000 mg in study ARGX-113-2002. The participant died due to renal cancer metastatic, and the cause of death was reported as cardiac arrest. The SAE of renal cancer metastatic was determined by the investigator to be not related to efgartigimod or other study procedures.

- One participant for whom COVID-19 vaccination status was not reported in the medical history died because of SAEs of COVID-19 and Respiratory failure.

The participant was diagnosed with myasthenia gravis in 2016. At the time of the SAE of COVID-19 and SAE of respiratory failure, the participant had received 24 doses and completed 6 cycles of efgartigimod IV in study

ARGX-113-1705 and had received 12 doses and completed 3 cycles of efgartigimod PH20 SC in the extension study (ARGX-113-2002) . The participant died on an unspecified date in February 2022 due to SAE of respiratory failure and SAE of COVID-19. These events were considered by the investigator to be not related to efgartigimod. As alternative causes, this was an elderly participant with important cardiovascular and metabolic concomitant conditions.

Other Serious Adverse Events

Studies ARGX-113-2001 and ARGX-113-2002

A summary of SAEs that occurred in ARGX-113-2001 and ARGX-113-2002 is provided by SOC and PT below.

Table 42: Studies ARGX-113-2001 and ARGX-113-2002: SAEs by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Study ARGX-113-2001				Study ARGX-113-2002							
					Antecedent study treatment assignment							
	EFG SC (N=55)		EFG IV (N=55)		SC 2001 (N=51)		IV 2001 (N=48)		IV 1705 (N=65)		Total (N=164)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 SAE	8 (14.5)	10	4 (7.3)	5	8 (15.7)	10	5 (10.4)	7	4 (6.2)	5	17 (10.4)	22
Nervous system disorders	6 (10.9)	7	1 (1.8)	1	4 (7.8)	5	1 (2.1)	1	2 (3.1)	2	7 (4.3)	8
Myasthenia gravis	5 (9.1)	5	1 (1.8)	1	4 (7.8)	5	1 (2.1)	1	1 (1.5)	1	6 (3.7)	7
Myasthenia gravis crisis	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Optic neuritis	1 (1.8)	1	0	...	0	...	0	...	0	...	0	...
Syncope	1 (1.8)	1	0	...	0	...	0	...	0	...	0	...
Infections and infestations	1 (1.8)	1	0	...	1 (2.0)	2	3 (6.3)	4	1 (1.5)	1	5 (3.0)	7
COVID-19	0	...	0	...	0	...	2 (4.2)	2	1 (1.5)	1	3 (1.8)	3
COVID-19 pneumonia	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Diarrhoea infectious	0	...	0	...	1 (2.0)	1	0	...	0	...	1 (0.6)	1
Pneumonia	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Rotavirus infection	0	...	0	...	1 (2.0)	1	0	...	0	...	1 (0.6)	1
Cellulitis	1 (1.8)	1	0	...	0	...	0	...	0	...	0	...
Respiratory, thoracic and mediastinal disorders	1 (1.8)	1	1 (1.8)	1	1 (2.0)	1	1 (2.1)	1	1 (1.5)	1	3 (1.8)	3
Respiratory failure	0	...	0	...	0	...	1 (2.1)	1	1 (1.5)	1	2 (1.2)	2
Dyspnoea	1 (1.8)	1	1 (1.8)	1	1 (2.0)	1	0	...	0	...	1 (0.6)	1

Injury, poisoning and procedural complications	1 (1.8)	1	0	...	2 (3.9)	2	0	...	0	...	2 (1.2)	2
Rib fracture	0	...	0	...	1 (2.0)	1	0	...	0	...	1 (0.6)	1
Spinal fracture	0	...	0	...	1 (2.0)	1	0	...	0	...	1 (0.6)	1
Humerus fracture	1 (1.8)	1	0	...	0	...	0	...	0	...	0	
Musculoskeletal and connective tissue disorders	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Back pain	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Renal cancer metastatic	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Cardiac disorders	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...
Cardiac failure congestive	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...
General disorders and administration site conditions	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...
Chest pain	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...
Reproductive system and breast disorders	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...
Testicular cyst	0	...	1 (1.8)	1	0	...	0	...	0	...	0	...

AE=adverse event; CSR=clinical study report; m=number of events; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IV=intravenous(ly); MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event;; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). The SC 2001 group refers to participants who received efgartigimod PH20 SC in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002.

8 (14.5%) participants had SAEs in the efgartigimod PH20 SC arm compared with 4 (7.3%) participants in the efgartigimod IV arm in study ARGX-113-2001. The most commonly reported SAE (≥5% of participants) was Myasthenia gravis which occurred in 5 (9.1%) participants in the efgartigimod PH20 SC arm and in 1 (1.8%) participant in the efgartigimod IV arm and thus contributed to the higher incidence of SAEs in the SC arm. None of the SAEs were considered by the investigator to be related to efgartigimod.

In study ARGX-113-2002, SAEs occurred in 17 (10.4%) participants in the total group. The most commonly reported SAEs (≥2 participants) were Myasthenia gravis (6 [3.7%]) participants), COVID-19 (3 [1.8%] participants), and Respiratory failure (2 [1.2%] participants). 1 SAE, a grade 3 Myasthenia gravis crisis event was considered related to efgartigimod PH20 SC.

SC Pooling Block

A summary of SAEs that occurred in the SC PB is provided by SOC and PT below

Table 43: SC Pooling Block: SAEs by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)	
	n (%)	m
≥1 SAE	23 (13.7)	33
Nervous system disorders	11 (6.5)	16
Myasthenia gravis	10 (6.0)	13
Myasthenia gravis crisis	1 (0.6)	1
Optic neuritis	1 (0.6)	1
Syncope	1 (0.6)	1
Infections and infestations	6 (3.6)	8
COVID-19	3 (1.8)	3
Cellulitis	1 (0.6)	1
COVID-19 pneumonia	1 (0.6)	1
Diarrhoea infectious	1 (0.6)	1
Pneumonia	1 (0.6)	1
Rotavirus infection	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	4 (2.4)	4
Dyspnoea	2 (1.2)	2
Respiratory failure	2 (1.2)	2
Injury, poisoning and procedural complications	3 (1.8)	3
Humerus fracture	1 (0.6)	1
Rib fracture	1 (0.6)	1
Spinal fracture	1 (0.6)	1
Musculoskeletal and connective tissue disorders	1 (0.6)	1
Back pain	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	1
Renal cancer metastatic	1 (0.6)	1

AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants for whom the observation was reported; N=number of participants in the analysis set; PT=Preferred Term; SAE=serious adverse event; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021).

SAEs occurred in 23 (13.7%) participants in the total group. SAE of Myasthenia gravis was reported in 10 (6.0%) participants. There were not observed any clinical meaningful differences between the SAEs reported in the SC pooling block and in the two studies ARGX-113-2001 and ARGX-113-2002.

IV Pooling Block

A summary of SAEs that occurred in the IV PB is provided by SOC and PT below.

Table 44: IV Pooling Block: SAEs by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total efgartigimod (N=164)	
	n (%)	m
≥1 SAE	38 (23.2)	56
Nervous system disorders	11 (6.7)	12
Myasthenia gravis	8 (4.9)	8
Myasthenia gravis crisis	2 (1.2)	2
Cerebral venous sinus thrombosis	1 (0.6)	1
Stupor	1 (0.6)	1
Infections and infestations	9 (5.5)	11
COVID-19	2 (1.2)	2
COVID-19 pneumonia	2 (1.2)	2
Pneumonia	2 (1.2)	2
Dysentery	1 (0.6)	1
Pneumonia escherichia	1 (0.6)	1
Pseudomonal sepsis	1 (0.6)	1
Septic shock	1 (0.6)	1
Urinary tract infection	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (3.7)	7
Adenocarcinoma of colon	1 (0.6)	1
Lung neoplasm malignant	1 (0.6)	1
Pancreatic carcinoma metastatic	1 (0.6)	1
Prostate cancer	1 (0.6)	1
Rectal adenocarcinoma	1 (0.6)	1
Squamous cell carcinoma of the vulva	1 (0.6)	1
Uterine leiomyoma	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	5 (3.0)	5
Acute respiratory failure	2 (1.2)	2
Asthma	1 (0.6)	1
Pneumonitis aspiration	1 (0.6)	1
Pulmonary embolism	1 (0.6)	1

Cardiac disorders	4 (2.4)	5
Acute myocardial infarction	1 (0.6)	1
Arrhythmia	1 (0.6)	1
Atrial fibrillation	1 (0.6)	1
Cardiac failure congestive	1 (0.6)	1
Defect conduction intraventricular	1 (0.6)	1
Blood and lymphatic system disorders	2 (1.2)	2
Anaemia	1 (0.6)	1
Thrombocytosis	1 (0.6)	1
Gastrointestinal disorders	2 (1.2)	2
Diarrhoea	1 (0.6)	1
Irritable bowel syndrome	1 (0.6)	1
Injury, poisoning and procedural complications	2 (1.2)	2
Infusion related reaction	1 (0.6)	1
Spinal compression fracture	1 (0.6)	1
Surgical and medical procedures	2 (1.2)	3
Shoulder arthroplasty	1 (0.6)	1
Spinal decompression	1 (0.6)	1
Spinal operation	1 (0.6)	1
Eye disorders	1 (0.6)	1
Retinal detachment	1 (0.6)	1
General disorders and administration site conditions	1 (0.6)	1
Death	1 (0.6)	1
Investigations	1 (0.6)	1
SARS-CoV-2 test positive	1 (0.6)	1
Metabolism and nutrition disorders	1 (0.6)	1
Type 1 diabetes mellitus	1 (0.6)	1
Psychiatric disorders	1 (0.6)	1
Depression	1 (0.6)	1
Renal and urinary disorders	1 (0.6)	1
Bladder neck obstruction	1 (0.6)	1
Vascular disorders	1 (0.6)	1
Shock	1 (0.6)	1

AE=adverse event; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PT=Preferred Term; SAE=serious adverse event; SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021).

SAEs occurred in 38 (23.2%) participants in the IV pooling block. Myasthenia gravis occurred in 8 (4.9%) participants. There were not observed any clinical meaningful differences between the SAEs reported in the IV pooling block and SC pooling block.

Adverse Events of Special Interest

SC Pooling Block

A summary of AESIs that occurred in the total group is presented by SOC and PT below

Table 45: SC Pooling Block: AESIs in the Total Group, by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)	
	n (%)	m
≥1 AESI[a]	57 (33.9)	91
Infections and infestations	57 (33.9)	91
COVID-19	21 (12.5)	22
Nasopharyngitis	11 (6.5)	13
Upper respiratory tract infection	7 (4.2)	7
Pharyngitis	4 (2.4)	4
Bronchitis	3 (1.8)	4
Gastroenteritis	3 (1.8)	3
Rhinitis	3 (1.8)	3
Sinusitis	3 (1.8)	3
Urinary tract infection	3 (1.8)	5
Gastroenteritis viral	2 (1.2)	2
Pneumonia	2 (1.2)	2
Viral upper respiratory tract infection	2 (1.2)	2
Acute sinusitis	1 (0.6)	1
Asymptomatic COVID-19	1 (0.6)	1
Cellulitis	1 (0.6)	1
COVID-19 pneumonia	1 (0.6)	1
Cystitis	1 (0.6)	1
Diarrhoea infectious	1 (0.6)	1
Gastrointestinal bacterial overgrowth	1 (0.6)	1
Gastrointestinal infection	1 (0.6)	1

Infection	1 (0.6)	1
Influenza	1 (0.6)	1
Injection site infection	1 (0.6)	1
Localised infection	1 (0.6)	1
Nasal herpes	1 (0.6)	1
Oral herpes	1 (0.6)	1
Otitis media acute	1 (0.6)	1
Peritonitis	1 (0.6)	1
Respiratory tract infection viral	1 (0.6)	1
Rotavirus infection	1 (0.6)	1
Sepsis	1 (0.6)	1
Tinea versicolour	1 (0.6)	1
Vaginal infection	1 (0.6)	1

AE=adverse event; AESI=adverse event of special interest; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants for whom the observation was reported; N=number of participants in the analysis set; PT=Preferred Term; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). a An AESI was defined as any AE in the MedDRA SOC Infections and infestations.

COVID-19–Relevant Events in the SC PB

COVID-19–relevant events are summarized below.

Table 46: SC Pooling Block: COVID-19–Relevant AEs by PT (Safety Analysis Set)

Participant no.	Cycle number[a]	Preferred term	Seriousness (yes/no)	Outcome	Severity	Causality	Action concerning IMP	Onset day vs first IMP intake[a]/ Start of the cycle/ Last IMP intake before onset	Duration (days)	Total IgG[b]	
										Actual value (mg/L)	% Change[a]
SC 2001											
0010111140	1	COVID-19	No	Rec	Gr 1	Not	Wit	3/3/3	17	7210	NA
0310001038	1	COVID-19	No	Rec	Gr 1	Not	NA	42/42/21	6	3320	−65.0
0310001088	3	COVID-19	No	Rec	Gr 2	Not	No	176/51/29	7	1910	−78.8
0320007008	6	COVID-19	No	Rec	Gr 3	Not	No	282/18/4	10	1620	−77.9
0320007032	4	Asymptomatic COVID-19	No	Rec	Gr 1	Not	No	229/45/24	11	3550	-66.8
0360013037	4	COVID-19	No	Rec	Gr 2	Not	No	253/64/43	…	1920	−63.0
0480024062	2	COVID-19	No	Rec	Gr 1	Not	Int	209/13/6	12	7530	−11.2
9950001115	2	COVID-19	No	Rec	Gr 2	Not	No	185/40/19	17	6760	−1.7
9950002044	2	COVID-19	No	Rec	Gr 1	Not	Int	77/7/7	72	10400	49.4
9950004145	2	COVID-19	No	Rec	Gr 1	Not	NA	121/50/30	9	1200	−76.9
IV 2001											
0010110006	5	COVID-19	No	Rec	Gr 1	Not	No	256/46/25	7	3250	−41.5
0010110078	2	COVID-19 pneumonia	Yes	Rec	Gr 2	Not	Int	60/5/5	6	6690	10.0
0340038113	2	COVID-19	No	Rec	Gr 1	Not	Int	92/36/15	29	5420	−11.7
9950001131	2	COVID-19	No	Rec	Gr 2	Not	No	73/22/2	6	9670	−15.9
9950001131	2	COVID-19	Yes	Recs	Gr 3	Not	NA	79/28/8	…	9670	−15.9
9950002045	2	COVID-19	Yes	…	Gr 3	Not	Int	186/81/60	>14	3380	−74.4
IV 1705											
BEL0001114	3	COVID-19	No	Rec	Gr 1	Not	No	161/22/1	7	9870	−9.4
GEO0001113	3	COVID-19	No	Rec	Gr 2	Not	No	223/63/42	…	6910	−14.2
GEO0001214	2	COVID-19	No	Rec	Gr 1	Not	No	104/26/2	14	11400	1.8
GEO0002153	3	COVID-19	Yes	Fat	Gr 5	Not	Wit	241/69/48[c]	59	7080	−14.3
GEO0003106	1	COVID-19	No	Rec	Gr 2	Not	Int	11/11/3	25	11000	NA
GEO0003127	2	COVID-19	No	Rec	Gr 1	Not	NA	238/35/14	10	7190	−21.9
POL0005015	1	COVID-19	No	Rec	Gr 2	Not	No	22/22/1	14	5130	NA
POL0005024	3	COVID-19	No	Rec	Gr 2	Not	No	141/29/8	9	6110	−1.6

AE=adverse event; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; Fat=fatal; Gr=grade; IgG=immunoglobulin gamma; IMP=investigational medicinal product; Int=drug interrupted; IV=intravenous(ly); NA=not applicable; No=dose not changed; Not=not related; PT=Preferred Term; Rec=recovered; Recs=recovered/resolved with sequelae; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); Wit=drug withdrawn Note: SC 2001 refers to the participants who received efgartigimod PH20 SC in the antecedent study ARGX-113-2001 and are receiving it in extension study ARGX-113-2002. IV 2001 and IV 1705 refer to the participants who received efgartigimod IV in the antecedent study ARGX-113-2001 or ARGX-113-1705, respectively, and are receiving efgartigimod PH20 SC in extension study ARGX-113-2002. a The value was recalculated according to the participant start date in ARGX-113-2001, for participants who received efgartigimod PH20 SC in ARGX-113-2001 and had a COVID-19–relevant event in ARGX-113-2002. b Last available non missing total IgG value and percent change before the start of the COVID-19–relevant event. c The onset dates and duration were calculated based on the imputation rules in Module 5.3.5.3, ARGX-113-9021-9031-ISS SAP, Section 4.1.2

AESIs occurred in 57 (33.9%) participants in the total group. The most frequently AESIs were COVID-19 (12.5%), Nasopharyngitis (6.5%), Upper respiratory tract infection (4.2%) and Pharyngitis (2.4%).

Serious AESIs occurred in 6 (3.6%) participants in the total group. Serious AESIs included COVID-19 in 3 (1.8%) participants. Cellulitis, COVID-19 pneumonia, Diarrhoea infectious, Pneumonia, and Rotavirus infection were reported in 1 (0.6%) participant each.

IV Pooling Block

A summary of AESIs in the total efgartigimod group is presented by SOC and PT below.

Table 47: IV Pooling Block: AESIs in the Total Efgartigimod Group by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total efgartigimod (N=164)	
	n (%)	m
≥1 AESI[a]	101 (61.6)	229
Infections and infestations	101 (61.6)	229
Nasopharyngitis	28 (17.1)	37
Urinary tract infection	19 (11.6)	27
COVID-19	18 (11.0)	18
Upper respiratory tract infection	13 (7.9)	18
Bronchitis	8 (4.9)	11
Herpes zoster	8 (4.9)	8
Influenza	5 (3.0)	5
Pharyngitis	5 (3.0)	5
Oral herpes	4 (2.4)	5
Ear infection	4 (2.4)	4
Pneumonia	4 (2.4)	4
Respiratory tract infection	4 (2.4)	4
Cystitis	3 (1.8)	4
Gastroenteritis	3 (1.8)	4
COVID-19 pneumonia	3 (1.8)	3
Gingivitis	3 (1.8)	3
Sinusitis	3 (1.8)	3

Skin infection	2 (1.2)	4
Asymptomatic bacteriuria	2 (1.2)	2
Conjunctivitis	2 (1.2)	2
Fungal infection	2 (1.2)	2
Gastroenteritis viral	2 (1.2)	2
Hordeolum	2 (1.2)	2
Pharyngitis streptococcal	2 (1.2)	2
Tinea versicolour	2 (1.2)	2
Tonsillitis	2 (1.2)	2
Tracheitis	2 (1.2)	2
Viral infection	2 (1.2)	2
Viral upper respiratory tract infection	2 (1.2)	2
Vulvovaginal mycotic infection	2 (1.2)	2
Candida infection	1 (0.6)	2
Mastitis	1 (0.6)	2
Acute sinusitis	1 (0.6)	1
Bacterial infection	1 (0.6)	1
Bacteriuria	1 (0.6)	1
Body tinea	1 (0.6)	1
Breast abscess	1 (0.6)	1
Candida cervicitis	1 (0.6)	1
Cervicitis	1 (0.6)	1
Coronavirus infection	1 (0.6)	1
Dysentery	1 (0.6)	1
Epididymitis	1 (0.6)	1
Eye infection	1 (0.6)	1
Fungal skin infection	1 (0.6)	1
Gastrointestinal candidiasis	1 (0.6)	1
Helicobacter infection	1 (0.6)	1

Laryngopharyngitis	1 (0.6)	1
Medical device site abscess	1 (0.6)	1
Nail bed infection	1 (0.6)	1
Oral candidiasis	1 (0.6)	1
Oropharyngeal candidiasis	1 (0.6)	1
Otitis media	1 (0.6)	1
Periodontitis	1 (0.6)	1
Pneumonia escherichia	1 (0.6)	1
Pseudomonal sepsis	1 (0.6)	1
Pyelonephritis chronic	1 (0.6)	1
Respiratory tract infection viral	1 (0.6)	1
Rhinitis	1 (0.6)	1
Rotavirus infection	1 (0.6)	1
Salpingo-oophoritis	1 (0.6)	1
Septic shock	1 (0.6)	1
Sialoadenitis	1 (0.6)	1
Subcutaneous abscess	1 (0.6)	1
Viral pharyngitis	1 (0.6)	1
Viral tracheitis	1 (0.6)	1
Vulvovaginal candidiasis	1 (0.6)	1

AE=adverse event; AESI=adverse event of special interest; m=number of events; IV=intravenous(ly); MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PT=Preferred Term; SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). a An AESI was defined as any AE in the MedDRA SOC Infections and infestations.

COVID-19–Relevant Events in the IV PB

COVID-19–relevant events are summarized in below.

Table 48: IV Pooling Block: COVID-19–Relevant AEs by PT (Safety Analysis Set)

Participant No.	Cycle number	Preferred term	Seriousness (Yes/No)	Outcome	Severity	Causality	Action concerning IMP	Onset day vs first IMP intake/ Start of the cycle/ Last IMP intake before onset	Duration (days)	Total IgG[a]	
										Actual value (mg/L)	% Change
CZE0004161	10	COVID-19	No	Rec	Gr 2	Not	No	545/34/13	11	5240	−16.3
CZE0005060	6	COVID-19 pneumonia	Yes	NRec[b]	Gr 5	Unl	Wit	485/56/35	35	5850	−29.1
CZE0005080	9	COVID-19	No	Rec	Gr 1	Not	Int	566/8/8	16	10300	−23.7
ITA0003033	6	COVID-19	No	Rec	Gr 1	Not	No	983/91/70	24	5760	−11.1
POL0001050	7	COVID-19	No	Rec	Gr 2	Not	Int	627/4/4	19	5600	13.1
POL0006042	9	COVID-19	No	Rec	Gr 2	Unl	No	659/99/78	16	9570	13.4
POL0007180	7	COVID-19	No	Rec	Gr 2	Not	No	425/19/5	11	5520	−44.4
RUS0002156	9	Coronavirus infection	No	Rec	Gr 2	Unl	No	483/27/7	24	3120	−62.9
RUS0002175	4	COVID-19	No	Rec	Gr 2	Not	No	770/567/567	35	8380	32.8
SRB0001129	4	COVID-19	Yes	Rec	Gr 3	Not	Int	266/51/1	16	7590	2.8
USA0001022	12	COVID-19	No	Rec	Gr 1	Not	No	1E3/26/7	9	10200	15.6
USA0007167	10	COVID-19	No	Rec	Gr 2	Not	No	502/12/5	17	7740	−16.5
USA0009111	6	COVID-19 pneumonia	Yes	Rec	Gr 4	Unl	Wit	323/43/22	19	3110	−61.1
USA0014098	12	COVID-19	No	Rec	Gr 1	Not	No	906/85/64	16	9410	18.1
USA0019054	2	COVID-19	No	Rec	Gr 1	Not	No	923/166/145	11	9030	−17.9
DNK0001062	17	COVID-19	No	…	Gr 1	Not	No	833/21/7	>1	5300	−5.4
GEO0002094	4	COVID-19	No	Rec	Gr 1	Not	No	331/38/17	40	3010	−45
GEO0003088	4	COVID-19	Yes	Rec	Gr 2	Not	NA	474/24/3	13	8930	−5.6
SRB0001134	1	COVID-19	No	Rec	Gr 2	Not	No	281/281/260	17	5990	11.1
SRB0001141	12	COVID-19	No	Rec	Gr 1	Not	Int	724/10/10	9	5000	3.5
SRB0001146	13	COVID-19	No	Rec	Gr 2	Not	Int	617/22/1	17	5600	−11.8
SRB0001146	13	COVID-19 pneumonia	No	Rec	Gr 2	Not	No	622/27/6	12	5600	−11.8
USA0006068	9	SARS-CoV-2 test positive	Yes	Rec	Gr 3	Not	No	486/31/11	13	3530	−33.1
USA0006069	6	Exposure to SARS-CoV-2	No	Rec	Gr 1	Not	No	298/12/4	1	2580	−68.7

AE=adverse event; Gr=grade; IgG=immunoglobulin gamma; IMP=investigational medicinal product; Int=drug interrupted; IV=intravenous(ly); NA=not applicable; No=dose not changed; Not=not related; NRec=not recovered; PT=Preferred Term; Rec=recovered; Unl=unlikely related; Wit=drug withdrawn a Last available nonmissing total IgG value and percent change before the start of the COVID-related event. b For this participant, the event Septic shock had an outcome of fatal (Module 5.3.5.2, ARGX-113-1705-IA4 CSR, Listing 16.2.7.3)

In the IV pooling block, 101 (61.6%) participants in the total efgartigimod group had AESIs. The most frequent AESIs were Nasopharyngitis (17.1%), Urinary tract infection (11.6%), COVID-19 (11.0%), Upper respiratory tract infection (7.9%), Bronchitis (4.9%), and Herpes zoster (4.9%).

Injection- and Infusion-Related Reactions

SC Pooling Block

Injection-related reactions reported within 48 hours of efgartigimod administration by MedDRA SOC and PT are summarized for the safety analysis set in table below

Table 49: SC Pooling Block: Injection-Related Reactions Within 48-Hours of Efgartigimod Administration, by MedDRA SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)	
	n (%)	m
≥1 Injection-related reaction[a]	65 (38.7)	259
General disorders and administration site conditions	59 (35.1)	242
Injection site erythema	41 (24.4)	142
Injection site pain	13 (7.7)	28
Injection site rash	11 (6.5)	17
Injection site swelling	9 (5.4)	21
Injection site oedema	4 (2.4)	16
Injection site mass	3 (1.8)	4
Injection site urticaria	3 (1.8)	4
Injection site inflammation	2 (1.2)	4
Oedema	2 (1.2)	2
Administration site pain	1 (0.6)	1
Infusion site rash[b]	1 (0.6)	1

System organ class Preferred term	Total (N=168)	
	n (%)	m
Injection site induration	1 (0.6)	1
Peripheral swelling	1 (0.6)	1
Skin and subcutaneous tissue disorders	11 (6.5)	12
Pruritus	4 (2.4)	4
Dermatitis	2 (1.2)	2
Dermatitis atopic	2 (1.2)	2
Circumoral swelling	1 (0.6)	1
Erythema	1 (0.6)	1
Rash	1 (0.6)	1
Rash macular	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	3 (1.8)	3
Dyspnoea	2 (1.2)	2
Cough	1 (0.6)	1
Eye disorders	1 (0.6)	1
Eyelid oedema	1 (0.6)	1
Gastrointestinal disorders	1 (0.6)	1
Mouth swelling	1 (0.6)	1

AE=adverse event; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants for whom the observation was reported; N=number of participants in the analysis set; PT=Preferred Term; SMQ=standardized MedDRA query; SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). There is overlap in the PTs for localized Injection site reactions by high level term (refer to Section 2.1.5.2) and the SMQs for the injection- or infusion-related reactions.
a 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.
b The PT term of Infusion site rash will be corrected to Injection site rash in a subsequent database update.

65 (38.7%) participants had injection-related reactions. Most injection-related reactions were localized Injection site reactions. All injection-related reactions were CTCAE grades 1 or 2, none were serious and there were no treatment discontinuations because of injection-related reactions.

The most commonly occurring injection-related reactions were Injection site erythema (24.4%), Injection site pain (7.7%), Injection site rash (6.5%), and Injection site swelling (5.4%). This is expected in an SC administered antibody.

IV Pooling Block

In the total efgartigimod group 18 (11.0%) participants had *Infusion-related reaction*. One (0.6%) participant had an infusion-related reaction that was serious (PT: *Infusion-related reaction*). No participants had an *Infusion-related reaction* that was CTCAE grade ≥3.

No *Anaphylactic reactions* or severe cases of *Hypersensitivity* occurred. Excluding localized *Injection site reactions*, AEs potentially associated with *Hypersensitivity* included *Rash* (4 [2.4%] participants); *Cough* and *Rash maculo-papular* (2 [1.2%] participants each).

Infusion-related reaction has been assessed in the initial MAA for efgartigimod IV formulation.

AEs of Myasthenia Gravis

Events in Study ARGX-113-2001

In study ARGX-113-2001, 6 (10.9%) participants treated with efgartigimod PH20 SC and 1 (1.8%) participant treated with efgartigimod IV reported AEs of Myasthenia gravis. Overall, Myasthenia gravis was reported in 10 (6.0%) participants in the SC polling block and 8 (4.9%) participants in the IV pooling block. In the initial MAA for the IV formulation, Myasthenia gravis occurred with similar frequency in the efgartigimod arm and placebo arm and was therefore not considered related to efgartigimod. Further, myasthenia gravis crisis is a known risk associated with myasthenia gravis with a reported incidence of 15-20% of myasthenic patients experiencing myasthenic crisis at least once in their lives.

The 5 out of 6 events related to SC formulation occurred during the 7-week posttreatment follow-up period. 2 out of 6 receiving SC formulation had a bodyweight >90 kg. However, those 2 participants had events that are known triggers for MG exacerbations: administration of high dose steroids and infection, which correlated temporally with their MG exacerbation. Body weight related to SAEs is further discussed in the relevant section. 4 participants had moderate to severe gMG (MGFA Class III or IV) at screening.

2.5.8.4. Laboratory findings

Studies ARGX-113-2001 and ARGX-113-2002

A summary of grade ≥3 abnormalities in clinical chemistry and hematology is presented in table below.

Table 50: Studies ARGX-113-2001 and ARGX-113-2002: Laboratory Abnormalities of CTCAE Grade ≥3 in All Cycles (Safety Analysis Set)

	Study ARGX-113-2001				Study ARGX-113-2002							
					Antecedent study treatment assignment							
	EFG SC (N=55)		EFG IV (N=55)		SC 2001 (N=51)		IV 2001 (N=48)		IV 1705 (N=65)		Total (N=164)	
	n/Na	%	n/Na	%	n/Na	%	n/Na	%	n/Na	%	n/Na	%
Chemistry												
Cholesterol high	0	…	0	…	0	…	0	…	1/60	1.7	1/158	0.6
Grade 3	0	…	0	…	0	…	0	…	1/60	1.7	1/158	0.6
GGT increased	1/55	1.8	1/55	1.8	1/51	2.0	0	…	0	…	1/160	0.6
Grade 3	1/55	1.8	1/55	1.8	1/51	2.0	0	…	0	…	1/160	0.6
Hyperkalemia	0	…	0	…	0	…	1/47	2.1	0	…	1/160	0.6
Grade 3	0	…	0	…	0	…	1/47	2.1	0	…	1/160	0.6
Hypertriglyceridemia	1/55	1.8	1/55	1.8	1/51	2.0	0	…	0	…	1/158	0.6
Grade 3	1/55	1.8	1/55	1.8	1/51	2.0	0	…	0	…	1/158	0.6
Hematology												
Activated partial thromboplastin time prolonged	0	…	1/55	1.8	0	…	1/47	2.1	0	…	1/160	0.6
Grade 3	0	…	1/55	1.8	0	…	1/47	2.1	0	…	1/160	0.6
Lymphocyte count decreased	3/55	5.5	2/55	3.6	5/51	9.8	2/47	4.3	6/62	9.7	13/160	8.1
Grade 3	3/55	5.5	2/55	3.6	5/51	9.8	2/47	4.3	5/62	8.1	12/160	7.5
Grade 4	0	…	0	…	0	…	0	…	1/62	1.6	1/160	0.6
Neutrophil count decreased	0	…	1/55	1.8	0	…	0	…	1/62	1.6	1/160	0.6
Grade 3	0	…	1/55	1.8	0	…	0	…	1/62	1.6	1/160	0.6
White blood cell decreased	0	…	1/55	1.8	0	…	0	…	0		0	…
Grade 3	0	…	1/55	1.8	0	…	0	…	0		0	…

CTCAE=Common Terminology Criteria for Adverse Events; EFG=efgartigimod; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; GGT=gamma-glutamyl transferase; IV=intravenous(ly); N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; Na=number of participants in the analysis set with data; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)
Note: The SC 2001 group refers to participants who received efgartigimod PH20 in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002.

In study ARGX-113-2001, 5 (4.5%) participants had grade 3 clinical laboratory abnormalities of lymphocyte count decreased. Of the 5 participants 1 participant in the efgartigimod PH20 SC arm had an AE of Rhinitis. The investigator did not consider the event to be related to efgartigimod.

In study ARGX-113-2002, 13 (8.1%) participants had a clinical laboratory abnormality of lymphocyte count decreased: grade 3 in 12 (7.5%) participants, and grade 4 in 1 (0.6%) participant. Among them, 2 participants also had treatment-related PTs of Lymphocyte count decreased. 2 grade 1 upper respiratory tract infections were reported as related to efgartigimod SC administration.

Hypertriglyceridemia were reported as grade 3 in 2 patients in study ARGX-113-2001 and in one patient in study ARGX-113-2002.

SC Pooling Block

A summary of grade ≥3 abnormalities in clinical chemistry and hematology is presented below

Table 51: SC Pooling Block: Laboratory Abnormalities of CTCAE Grade ≥3 Reported in the Total Group (Safety Analysis Set)

	Total (N=168)	
	n/N[a]	%
Chemistry		
Hyperkalemia	1/164	0.6
Grade 3	1/164	0.6
Cholesterol high	1/162	0.6
Grade 3	1/162	0.6
Hypertriglyceridemia	1/162	0.6
Grade 3	1/162	0.6
Hematology		
Lymphocyte count decreased	13/164	7.9
Grade 3	12/164	7.3
Grade 4	1/164	0.6
Neutrophil count decreased	1/164	0.6
Grade 3	1/164	0.6

CTCAE=Common Terminology Criteria for Adverse Events; GGT=gamma-glutamyl transferase; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; Na=number of participants in the analysis set with data; SC=subcutaneous(ly)

Grade 3 lymphocyte count decreased was reported in 12 (7.3%) participants and grade 4 lymphocyte count decreased in 1 (0.6%) participant.

High cholesterol and hypertriglyceridemia were reported in 1 patient each (0.6%).

IV Pooling Block

A summary of grade ≥3 abnormalities in clinical chemistry and hematology is presented below.

Table 52: IV Pooling Block: Laboratory Abnormalities of CTCAE Grade ≥3 Reported in the Total Efgartigimod Group (Safety Analysis Set)

	Total efgartigimod (N=164) n/N (%)
Chemistry	
Creatinine increased	1/162 (0.6)
Grade 3	1/162 (0.6)
Cholesterol high	2/148 (1.4)
Grade 3	2/148 (1.4)
Hypertriglyceridemia	6/148 (4.1)
Grade 3	6/148 (4.1)
Hypernatremia	2/162 (1.2)
Grade 3	1/162 (0.6)
Grade 4	1/162 (0.6)
Hematology	
Activated partial thromboplastin time prolonged	1/162 (0.6)
Grade 3	1/162 (0.6)
White blood cell decreased	1/162 (0.6)
Grade 3	1/162 (0.6)
Lymphocyte count decreased	19/162 (11.7)
Grade 3	17/162 (10.5)
Grade 4	2/162 (1.2)
Neutrophil count decreased	2/162 (1.2)
Grade 3	2/162 (1.2)

CTCAE=Common Terminology for Adverse Events; IV=intravenous(ly); N=number of participants in the analysis set with data n=number of participants for whom the observation was reported;

Grade 4 laboratory abnormalities were reported for lymphocyte count decreased in 2 (1.2%) participants and hypernatremia in 1 (0.6%) participant. Grade 3 lymphocyte count decreased were reported in 19 (11.7%) participants.

Grade 3 hypertriglyceridemia were reported in 6 (4.1%) participants and grade 3 cholesterol in 2 (1.4%) participants.

Vital Signs and Physical Examination

Studies ARGX-113-2001 and ARGX-113-2002

Overall, there were no notable changes from baseline in vital sign parameters (heart rate, systolic and diastolic blood pressure) in both studies and data were similar to the data shown in the initial MAA (data not shown but available in Clinical study reports).

Electrocardiogram

Studies ARGX-113-2001 and ARGX-113-2002

A summary of participants with severe abnormalities in electrocardiogram (ECG) evaluations in ARGX-113-2001 and ARGX-113-2002 is presented below.

Table 53: Studies ARGX-113-2001 and ARGX-113-2002: Most Severe Abnormalities in Electrocardiogram Parameters in Any Cycle (Safety Analysis Set)

	Study ARGX-113-2001				Study ARGX-113-2002							
					Antecedent study treatment assignment							
	EFG SC (N=55)		EFG IV (N=55)		SC 2001 (N=51)		IV 2001 (N=48)		IV 1705 (N=65)		Total (N=164)	
	n/N[a]	%	n/N[a]	%	n/N[a]	%	n/N[a]	%	n/N[a]	%	n/N[a]	%
Heart rate (bpm)												
Low (<40)	0	…	1/55	1.8	0	…	1/47	2.1	0	…	1/60	0.6
High (>100)	1/54	1.9	0	…	0	…	1/47	2.1	3/62	4.8	4/60	2.5
PR interval (ms)												
Low (<120)	1/53	1.9	3/53	5.7	2/50	4.0	3/46	6.5	4/62	6.5	9/158	5.7
High (>220)	0	…	1/53	1.9	1/50	2.0	3/46	6.5	0	…	4/158	2.5
QRS duration (ms)												
High (>120)	2/54	3.7	4/55	7.3	1/51	2.0	3/47	6.4	1/62	1.6	5/160	3.1
QTcF interval (ms)												
]450; 480]	1/54	1.9	2/55	3.6	2/51	3.9	4/47	8.5	4/62	6.5	10/160	6.3
]480; 500]	0	…	1/55	1.8	0	…	0	…	0	…	0	…
Change from baseline of]30; 60]	3/54	5.6	3/55	5.5	2/51	3.9	8/47	17.0	5/46	10.9	15/144	10.4

bpm=beats per minute; CSR=clinical study report; EFG=efgartigimod; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IV=intravenous(ly); N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; Na=number of participants in the analysis set with data; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly) Note: The SC 2001 group refers to participants who received efgartigimod PH20 in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002.

SC Pooling Block

A summary of participants with ECG abnormalities is presented below.

Table 54: SC Pooling Block: Abnormalities in Electrocardiogram Parameters Reported in the Total Group (Safety Analysis Set)

	Total (N=168)	
	n/Na	%
HR (bpm)		
Low	1/163	0.6
High	6/163	3.7
PR (ms)		
Low	11/161	6.8
High	4/161	2.5
QRS (ms)		
High	6/163	3.7
QTcF (ms)		
]450; 480]	11/163	6.7
QTcF change (ms)		
]30; 60]	25/163	15.3
>60	1[a]/163	0.6

bpm=beats per minute; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; HR=heart rate; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; Na=number of participants in the analysis set with data; PR=PR interval; QRS=duration of ventricular depolarization; QTcF=rate-corrected QT intervals using Fridericia's formula; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly) a This QTcF change from baseline occurred before the first dose of efgartigimod PH20 SC in study ARGX-113-2002. Accordingly, this event was not captured in the ARGX-113-2001 CSR or ARGX-113-2002-IA1 CSR

IV Pooling Block

A summary of participants with ECG abnormalities is presented below.

Table 55: IV Pooling Block: Abnormalities in Electrocardiogram Parameters Reported in the Total Efgartigimod Group (Safety Analysis Set)

	Total efgartigimod (N=164) n/N (%)
HR (bpm)	
High	10/164 (6.1)
PR (ms)	
Low	19/163 (11.7)
High	5/163 (3.1)
QRS (ms)	
High	12/164 (7.3)
QTcF (ms)	
]450; 480]	20/164 (12.2)
]480; 500]	4/164 (2.4)
]30; 60]	40/164 (24.4)
>60	2/164 (1.2)

bpm=beats per minute; HR=heart rate; IV=intravenous(ly); N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PR=PR interval; QRS=duration of ventricular depolarization; QT=total duration of ventricular depolarization; QTcF=rate-corrected QT intervals using Fridericia's formula. Note: Most severe abnormalities considering all postbaseline assessments (all cycles), including unscheduled assessments

Suicidality Assessment

A prospective assessment for suicidal ideation and behavior was included in ARGX-113-1602, ARGX-113-1704, ARGX-113-1705, ARGX-113-2001, and ARGX-113-2002. This suicidality assessment was made by asking the participant the following question from the PHQ-9: "Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?"

The suicidality assessment is in line with the suicidality assessment from the initial MAA for the IV formulation and does not raise any concerns regarding efgartigimod SC.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable. There are no in vitro biomarker tests relevant for patient selection for safety.

2.5.8.6. Safety in special populations

Age

Review of Demographic and baseline disease characteristics by age showed that the majority of participants were 18 to <65 years and were female (78.6%). The mean (SD) time since diagnosis was longer in the 18 to <65 years category (9.39 [8.646] years), than the ≥65 years category (6.12 [4.345] years). The percentage of participants who received concomitant treatment for gMG at baseline with NSIDs and steroids was higher in the 18 to <65 years category (41.7%) than the ≥65 years category (27.8%). The majority of participant had normal renal function in the 18 to <65 years category (90.2%) and mild renal impairment in the ≥65 years category (63.9%).

Two deaths occurred in participants ≥65 years; however, for both participants, the cause of death was not considered by the investigator to be related to efgartigimod.

Table 56: Adverse Events overview by age categories: all participants (Ach-R seropositive and seronegative) with gMG who received efgartigimod PH20 SC (any cycle)

	TOTAL (N=168)					
	18 - <65 years (N=132)			>=65 years (N=36)		
TOTAL NUMBER OF PARTICIPANTS WITH:	n	(%)	m	n	(%)	m
AT LEAST ONE TEAE	107	(81.1)	773	25	(69.4)	166
AT LEAST ONE SERIOUS TEAE	15	(11.4)	22	8	(22.2)	11
AT LEAST ONE GRADE >= 3 TEAE	18	(13.6)	31	8	(22.2)	22
AT LEAST ONE FATAL TEAE	0			2	(5.6)	3
AT LEAST ONE TREATMENT-RELATED TEAE ACCORDING TO PI	73	(55.3)	407	14	(38.9)	46
AT LEAST ONE SERIOUS TREATMENT-RELATED TEAE	0			1	(2.8)	1
AT LEAST ONE TEAE LEADING TO INTERRUPTION OF STUDY DRUG	9	(6.8)	10	5	(13.9)	11
AT LEAST ONE TEAE LEADING TO DISCONTINUATION OF STUDY DRUG	1	(0.8)	1	4	(11.1)	5
AT LEAST ONE TEAE OF SPECIAL INTEREST	47	(35.6)	73	10	(27.8)	18
AT LEAST ONE INJECTION-RELATED REACTION	53	(40.2)	236	12	(33.3)	23
AT LEAST ONE TREATMENT-EMERGENT INJECTION SITE REACTION	62	(47.0)	318	12	(33.3)	29

n= number of participants with event (participants with multiple events within the same category are counted only once)
m = number of events, TEAE=treatment-emergent adverse event, PI = Principal investigator.
The denominator for the percentage calculations is N: the total number of participants in the safety analysis set per treatment, cycle and subgroup
Treatment-related is defined as at least possible drug related according to the investigator or a missing drug relatedness

Body Weight

Baseline body weight ranged from 42.0 to 150.2 kg for participants in the efgartigimod PH20 SC arm of ARGX-113-2001.

Post hoc analyses were performed for AEs by baseline weight of participants in the SC PB. No clinically meaningful differences in the safety profiles of efgartigimod PH20 SC were identified across the baseline body weight categories (ie, <50 kg, ≥50 to <75 kg, ≥75 to <100 kg, ≥100 to <125 kg, or ≥125 kg). The frequency of grade ≥3 AEs and SAEs in the ≥100 to <125 kg body weight category was higher than in the other weight categories; however, there were a small number of participants in each body weight category.

Myasthenia gravis exacerbation was reported in three patients in the ≥100 to <125 kg body weight category.

Table 57: Adverse Events overview by weight group: all participants (Ach-R seropositive and seronegative) with gMG who received efgartigimod PH20 SC

	EFG SC									
	< 50 KG		50 TO <75 KG		75 TO <100 KG		100 TO <125 KG		>= 125 KG	
	(N=7)		(N=70)		(N=65)		(N=22)		(N=4)	
TOTAL NUMBER OF PARTICIPANTS WITH:	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
AT LEAST ONE TEAE	6 (85.7)	49	58 (82.9)	403	48 (73.8)	340	17 (77.3)	130	3 (75.0)	17
AT LEAST ONE SERIOUS TEAE	0		4 (5.7)	7	10 (15.4)	14	8 (36.4)	11	1 (25.0)	1
AT LEAST ONE GRADE >= 3 TEAE	0		7 (10.0)	10	10 (15.4)	15	8 (36.4)	27	1 (25.0)	1
AT LEAST ONE FATAL TEAE	0		0		1 (1.5)	2	1 (4.5)	1	0	
AT LEAST ONE TREATMENT-RELATED TEAE ACCORDING TO PI	4 (57.1)	16	39 (55.7)	248	31 (47.7)	150	10 (45.5)	27	3 (75.0)	12
AT LEAST ONE SERIOUS TREATMENT-RELATED TEAE	0		0		1 (1.5)	1	0		0	
AT LEAST ONE TEAE LEADING TO INTERRUPTION OF STUDY DRUG	1 (14.3)	1	5 (7.1)	5	4 (6.2)	5	4 (18.2)	10	0	
AT LEAST ONE TEAE LEADING TO DISCONTINUATION OF STUDY DRUG	0		0		3 (4.6)	4	2 (9.1)	2	0	
AT LEAST ONE TEAE OF SPECIAL INTEREST	3 (42.9)	3	22 (31.4)	28	21 (32.3)	36	9 (40.9)	22	2 (50.0)	2
AT LEAST ONE INJECTION-RELATED REACTION	3 (42.9)	9	29 (41.4)	160	22 (33.8)	72	9 (40.9)	16	2 (50.0)	2
AT LEAST ONE TREATMENT-EMERGENT INJECTION SITE REACTION	4 (57.1)	11	32 (45.7)	187	26 (40.0)	116	10 (45.5)	21	2 (50.0)	12

n= number of participants with event (participants with multiple events within the same category are counted only once)

m = number of events, TEAE=treatment-emergent adverse event, PI = Principal investigator.
The denominator for the percentage calculations is N: the total number of participants in the safety analysis set per treatment, cycle and subgroup
Treatment-related is defined as at least possible drug related according to the investigator or a missing drug relatedness

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.

Although allowed per study inclusion and exclusion criteria, participants with hepatic impairment have not been enrolled in an efgartigimod clinical study. Therefore, no clinical data in participants with hepatic impairment are available. The impact of hepatic impairment on the PK and PD of efgartigimod has not been studied; however, it unlikely that a dose adjustment is needed for participants with hepatic impairment.

Markers of hepatic function were evaluated as potential covariates in the population PK/PD analysis. Albumin, total bilirubin, AST, ALP, and ALT did not influence any of the model parameters in the final population PK/PD model.

Renal Impairment

The overall safety profile was similar between participants with normal renal function and those with mild renal impairment (Table 51). The frequency of participants with SAEs, AEs grade ≥3, and AEs leading to discontinuation was higher in participants with mild renal impairment than those with normal renal function.

Table 58: SC Pooling Block: Overview of Adverse Events in the Total Group, by Estimated Glomerular Filtration Rate Value at Baseline (Safety Analysis Set)

	Total (N=168)							
	Normal renal function[a] (N=129)		Mild renal impairment[b] (N=35)		Moderate renal impairment[c] (N=3)		Severe renal impairment[d] (N=1)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Overall								
≥1 AE	100 (77.5)	707	29 (82.9)	221	2 (66.7)	5	1 (100)	6
≥1 SAE	14 (10.9)	22	9 (25.7)	11	0	…	0	…
≥1 AE of CTCAE grade ≥3	15 (11.6)	35	10 (28.6)	17	0	…	1 (100)	1

AE=adverse event; AESI=adverse event of special interest; CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants for whom the observation was reported; N=number of participants in the analysis set per eGFR value at baseline; PI=principal investigator; SAE=serious adverse event; SMQ=standardized MedDRA query; SOC=System Organ Class
a Normal renal function is defined as an eGFR value of ≥90 mL/min/1.73m^2.
b Mild renal impairment is defined as an eGFR value that is ≥60 mL/min/1.73m^2 to <90 mL/min/1.73m^2.
c Moderate renal impairment is defined as eGFR value that is ≥30 mL/min/1.73m^2 to <60 mL/min/1.73m^2.
d Severe renal impairment is defined as eGFR value that is <30 mL/min/1.73m^2.
e An AESI was defined as any AE in the MedDRA SOC Infections and infestations.
F 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.
G Injection site reactions were defined as AEs with MedDRA high level term Injection site reactions regardless of the time of AE onset relative to an injection. There is overlap in the PTs for localized Injection site reactions by high level term the SMQs for the injection- or infusion-related reactions.

2.5.8.7. Immunological events

The participant classification, incidence, and prevalence of ADA against efgartigimod during the study are summarized for the overall population in table below.

Table 59: Participant classification, incidence, and prevalence of ADA against Efgartigimod in Study ARGX-113-2001 in the overall population (safety analysis set)

	EFG SC (N=55) n (%)	EFG IV (N=55) n (%)	Total (N=110) n (%)
ADA-evaluable/unevaluable participants			
ADA evaluable participants	55 (100)	55 (100)	110 (100)
ADA unevaluable participants	0	0	0
Baseline ADA sample status			
ADA positive	7 (12.7)	5 (9.1)	12 (10.9)
ADA negative	48 (87.3)	50 (90.9)	98 (89.1)
ADA participant classification			
ADA positive	19 (34.5)	11 (20.0)	30 (27.3)
Treatment-boosted ADA	1 (1.8)	1 (1.8)	2 (1.8)
Treatment-induced ADA	18 (32.7)	10 (18.2)	28 (25.5)
ADA negative	36 (65.5)	44 (80.0)	80 (72.7)
Treatment-unaffected ADA	6 (10.9)	4 (7.3)	10 (9.1)
ADA negative	30 (54.5)	40 (72.7)	70 (63.6)
Incidence/prevalence			
ADA incidence	19 (34.5)	11 (20.0)	30 (27.3)
ADA prevalence	25 (45.5)	15 (27.3)	40 (36.4)

Source: Module 5.3.5.1, ARGX-113-2001 CSR, Table 14.2.9.3
ADA=antidrug antibody; CSR=clinical study report; EFG=efgartigimod; IV=intravenous; n=number of participants for whom the observation was reported; N=number of participants per arm in the analysis set; SC=subcutaneous

The participant classification, incidence, and prevalence of NAb against efgartigimod for the overall population are presented below.

Table 60: Participant classification, incidence, and prevalence of NAb against Efgartigimod in Study ARGX-113-2001 in the overall population (safety analysis set)

	EFG SC (N=55) n (%)	EFG IV (N=55) n (%)	Total (N=110) n (%)
NAb-evaluable/unevaluable participants			
NAb evaluable participants	55 (100)	55 (100)	110 (100)
NAb unevaluable participants	0	0	0
Baseline NAb sample status			
NAb negative	55 (100)	55 (100)	110 (100)
NAb positive	0	0	0
NAb participant classification			
NAb negative	53 (96.4)	53 (96.4)	106 (96.4)
Baseline negative - postbaseline negative	53 (96.4)	53 (96.4)	106 (96.4)
Baseline positive - postbaseline negative	0	0	0
NAb positive	2 (3.6)	2 (3.6)	4 (3.6)

Baseline negative - postbaseline positive	2 (3.6)	2 (3.6)	4 (3.6)
Baseline positive - postbaseline positive	0	0	0
Incidence/prevalence			
NAb incidence	2 (3.6)	2 (3.6)	4 (3.6)
NAb prevalence	2 (3.6)	2 (3.6)	4 (3.6)

Source: Module 5.3.5.1, ARGX-113-2001 CSR, Table 14.2.9.13
CSR=clinical study report; EFG=efgartigimod; IV=intravenous; n=number of participants for whom the observation was reported; N=number of participants per arm in the analysis set, which is the denominator for the percentage calculation; NAb=neutralizing antibody; SC=subcutaneous

Impact of Retreatment on ADA Against Efgartigimod

In general, in the integrated analysis, the highest ADA incidence was observed in the first treatment cycle. The ADA incidence in participants who had at least 3 treatment cycles (ie, cohort 3; n=44) was 17 (38.6%), 6 (15.0%), and 3 (9.4%) in cycles 1, 2, and 3, respectively (table below). The cumulative ADA incidence over cycles 1 to 3 was 17 (38.6%). There were no additional participants classified as ADA positive during cycles 2 or 3 compared to cycle 1. Moreover, the number of participants classified as positive for ADA decreased in subsequent cycles, indicating that many of the ADA responses are transient.

NAb were detected during the first cycle and not during subsequent cycles for the 2 participants who were classified as NAb positive.

Table 61: Participant classification, incidence, and prevalence of ADA against Efgartigimod

	Cycle 1 (N=44) n (%)	**Cycle 2 (N=44) n (%)**	**Cycle 3 (N=44) n (%)**	**Any cycle up to cycle 3 (N=44) n (%)**
ADA evaluable participants	44 (100)	40 (90.9)	32 (72.7)	44 (100)
ADA unevaluable participants	0	4 (9.1)	12 (27.3)	0
Baseline ADA sample status				
Sample negative for ADA	39 (88.6)	36 (90.0)	28 (87.5)	39 (88.6)
Sample positive for ADA	5 (11.4)	4 (10.0)	4 (12.5)	5 (11.4)
ADA participant classification				
ADA negative	27 (61.4)	34 (85.0)	29 (90.6)	27 (61.4)
ADA negative	23 (52.3)	30 (75.0)	25 (78.1)	23 (52.3)
Treatment-unaffected ADA	4 (9.1)	4 (10.0)	4 (12.5)	4 (9.1)
ADA positive	17 (38.6)	6 (15.0)	3 (9.4)	17 (38.6)

Treatment-induced ADA	16 (36.4)	6 (15.0)	3 (9.4)	16 (36.4)
Treatment-boosted ADA	1 (2.3)	0	0	1 (2.3)
Incidence/prevalence				
ADA incidence	17 (38.6)	6 (15.0)	3 (9.4)	17 (38.6)
ADA prevalence	21 (47.7)	10 (25.0)	7 (21.9)	21 (47.7)

Source: Table 14.2.4.2.2
ADA=antidrug antibody; N=number of participants in the analysis set; n=number of participants for whom the observation was reported

Impact of ADA Against Efgartigimod on Safety

In both the efgartigimod PH20 SC and the efgartigimod IV arms, there was no apparent difference observed in the overall safety profile (AE or SAE) between the ADA negative participants and participants with treatment-induced, treatment-boosted, or treatment-unaffected ADA against efgartigimod.

Overall, AEs were reported in 37 (67.3%) participants in the efgartigimod PH20 SC arm. These AEs occurred in 63.3% (19) of participants who were ADA negative, 83.3% (5) of participants with treatment-unaffected ADA, 66.7% (12) of participants with treatment-induced ADA, and 100% (1) of participants with treatment-boosted ADA.

AEs were reported in 28 (50.9%) participants in the efgartigimod IV arm. These AEs occurred in 47.5% (19) of ADA-negative participants and in 50.0% (2), 60.0% (6), and 100% (1) of participants with treatment-unaffected, treatment-induced, and treatment-boosted ADA, respectively.

SAEs were reported in 8 (14.5%) participants in the efgartigimod PH20 SC arm. These SAEs occurred in 16.7% (5) of ADA-negative participants and in 16.7% (1), 11.1% (2), and 0% (0) of participants with treatment-unaffected, treatment-induced, and treatment-boosted ADA, respectively.

Overall, there was no apparent impact of ADA and NAb against efgartigimod on safety observed in either the efgartigimod PH20 SC arm or the efgartigimod IV arm; however, the data should be interpreted with caution given the limitations of this study (ie, small sample size and short study duration).

Prevalence and Incidence of Ab Against rHuPH20

The participant classification, incidence, and prevalence of Ab against rHuPH20 during the study are summarized for the overall population below.

Table 62: Participant classification, incidence, and prevalence of Ab against rHuPH20 in Study ARGX-113-2001 in the overall population (safety analysis set)

	EFG SC (N=55) n (%)
rHuPH20 Ab-evaluable/unevaluable participants	
rHuPH20 Ab evaluable participants	55 (100)
rHuPH20 Ab unevaluable participants	0
Baseline rHuPH20 Ab sample status	
rHuPH20 Ab negative	49 (89.1)
rHuPH20 Ab positive	6 (10.9)
rHuPH20 Ab participant classification	
rHuPH20 Ab negative	52 (94.5)
Treatment-unaffected rHuPH20 Ab	5 (9.1)
rHuPH20 Ab negative	47 (85.5)
rHuPH20 Ab positive	3 (5.5)
Treatment-boosted rHuPH20 Ab	1 (1.8)
Treatment-induced rHuPH20 Ab	2 (3.6)
Incidence/prevalence	
rHuPH20 Ab incidence	3 (5.5)
rHuPH20 Ab prevalence	8 (14.5)

Source: Module 5.3.5.1, ARGX-113-2001 CSR, Table 14.2.9.8.
Ab=antibody(ies); EFG=efgartigimod; N=number of participants per arm in the analysis set; n=number of participants for whom the observation was reported, which is the denominator for the percentage calculation rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

Impact of Retreatment on Ab Against rHuPH20

The incidence of Ab against rHuPH20 showed a minor increase across the cycles, with incidences of 5.5%, 6.7%, and 12.5% in cycles 1, 2, and 3, respectively; however, the incidence of Ab against rHuPH20 across all treatment cycles cumulatively remained low (14.5%) (table below).

Table 63: Participant classification, incidence, and prevalence of Ab against rHuPH20 in the pooled immunogenicity data of Studies ARGX-113-2001 and ARGX-113-2002 over all cycles cumulatively (safety analysis set)

	SC (2001) – SC (2002)			
	Cycle 1 (N=55) n (%)	**Cycle 2 (N=51) n (%)**	**Cycle 3 (N=44) n (%)**	**Any cycle (N=55) n (%)**
rHuPH20 Ab evaluable participants	55 (100)	45 (88.2)	32 (72.7)	55 (100)
rHuPH20 Ab unevaluable participants	0	6 (11.8)	12 (27.3)	0
Baseline Ab against rHuPH20 sample status				
Sample negative for Ab against rHuPH20	49 (89.1)	39 (86.7)	27 (84.4)	49 (89.1)
Sample positive for Ab against rHuPH20	6 (10.9)	6 (13.3)	5 (15.6)	6 (10.9)
rHuPH20 Ab participant classification				
Negative for Ab against rHuPH20	52 (94.5)	42 (93.3)	28 (87.5)	47 (85.5)
Negative for Ab against rHuPH20	47 (85.5)	37 (82.2)	24 (75.0)	43 (78.2)
Treatment-unaffected Ab against rHuPH20	5 (9.1)	5 (11.1)	4 (12.5)	4 (7.3)
Positive for Ab against rHuPH20	3 (5.5)	3 (6.7)	4 (12.5)	8 (14.5)
Treatment-induced Ab against rHuPH20	2 (3.6)	2 (4.4)	3 (9.4)	6 (10.9)
Treatment-boosted Ab against rHuPH20	1 (1.8)	1 (2.2)	1 (3.1)	2 (3.6)
Incidence/prevalence				
Incidence of Ab against rHuPH20	3 (5.5)	3 (6.7)	4 (12.5)	8 (14.5)
Prevalence of Ab against rHuPH20	8 (14.5)	8 (17.8)	8 (25.0)	12 (21.8)

Source: Table 14.2.5.2.1
2001=ARGX-113-2001; 2002=ARGX-113-2002; Ab=antibody(ies); CSR=clinical study report; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

Impact of Ab Against rHuPH20 on Efgartigimod PH20 SC Safety

There was no apparent difference observed in the overall safety profile (AE or SAE) between the participants negative for Ab against rHuPH20 participants and participants with treatment-induced, treatment-boosted, or treatment-unaffected Ab against rHuPH20.

During a post hoc analysis, injection site reactions were observed in 21 (38.2%) participants in the efgartigimod PH20 SC arm. These injection site reactions occurred in 18 (38.3%) participants who were negative for Ab against rHuPH20 and in 3 (60.0%) participants with treatment-unaffected Ab against rHuPH20. There were no injection site reactions in participants with treatment-induced or treatment-boosted Ab against rHuPH20.

Overall, there was no observed apparent impact of Ab against rHuPH20 on the safety of efgartigimod PH20 SC.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Clinical drug interactions 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).

Participants with gMG included in the phase 3 clinical development program were required to be on a stable dose of their concomitant MG therapy before screening, limited to acetylcholinesterase inhibitors, steroids, and NSIDs. NSIDs or steroids were allowed during the clinical studies in participants with gMG and were extensively used in the study populations; therefore, any potential interaction is accounted for in the safety profile. The effect of MG concomitant treatment of steroids and/or NSIDs was evaluated by means of covariate testing in the population PK/PD analysis. Although this covariate was statistically significant in the model, it was not considered to be clinically relevant.

In ARGX-113-2001, PLEX, Ig therapy (IVIg and SCIg), immunoadsorption, or a change in dosage or type of corticosteroid were prohibited. If specific protocol-defined criteria were met, these therapies were considered rescue therapy and could be used, but resulted in IMP discontinuation in ARGX-113-2001. The participants could roll over to ARGX-113-2002. Throughout ARGX-113-2002, treatment with PLEX, Ig therapy, or immunoadsorption (as a combination or monotherapy) was permitted as rescue therapy a maximum of 3 times per year, if it was not for a life-threatening condition and protocol-defined criteria were met.

Analysis of AESIs by concomitant treatment for gMG with steroids, NSIDs, steroids and NSIDs, or without any of these concomitant medications identified no meaningful differences between these groups, up to the data cutoff dates for this application (table below).

Table 64: SC Pooling Block: AESIs in the Total Efgartigimod Group in Any Concomitant MG Therapy Category at Baseline by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)							
	NSID only (N=21)		Steroids only (N=46)		NSID + steroids (N=65)		No NSID/steroids (N=36)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AESI[a]	7 (33.3)	13	18 (39.1)	25	22 (33.8)	36	10 (27.8)	17
Infections and infestations	7 (33.3)	13	18 (39.1)	25	22 (33.8)	36	10 (27.8)	17
COVID-19	2 (9.5)	2	10 (21.7)	10	4 (6.2)	4	5 (13.9)	6
Cellulitis	1 (4.8)	1	0	…	0	…	0	…
COVID-19 pneumonia	1 (4.8)	1	0	…	0	…	0	…
Cystitis	1 (4.8)	1	0	…	0	…	0	…
Gastroenteritis viral	1 (4.8)	1	0	…	1 (1.5)	1	0	…
Localised infection	1 (4.8)	1	0	…	0	…	0	…
Nasopharyngitis	1 (4.8)	3	1 (2.2)	1	8 (12.3)	8	1 (2.8)	1
Rhinitis	1 (4.8)	1	0	…	1 (1.5)	1	1 (2.8)	1
Sepsis	1 (4.8)	1	0	…	0	…	0	…
Upper respiratory tract infection	1 (4.8)	1	1 (2.2)	1	4 (6.2)	4	1 (2.8)	1
Acute sinusitis	0	…	0	…	0	…	1 (2.8)	1
Asymptomatic COVID-19	0	…	0	…	1 (1.5)	1	0	…
Bronchitis	0	…	0	…	2 (3.1)	3	1 (2.8)	1
Diarrhoea infectious	0	…	0	…	1 (1.5)	1	0	…
Gastroenteritis	0	…	2 (4.3)	2	1 (1.5)	1	0	…
Gastrointestinal bacterial overgrowth	0	…	1 (2.2)	1	0	…	0	…
Gastrointestinal infection	0	…	0	…	1 (1.5)	1	0	…
Infection	0	…	0	…	0	…	1 (2.8)	1
Influenza	0	…	0	…	1 (1.5)	1	0	…
Injection site infection	0	…	0	…	1 (1.5)	1	0	…
Nasal herpes	0	…	1 (2.2)	1	0	…	0	…
Oral herpes	0	…	1 (2.2)	1	0	…	0	…
Otitis media acute	0	…	0	…	1 (1.5)	1	0	…
Peritonitis	0	…	0	…	0	…	1 (2.8)	1
Pharyngitis	0	…	1 (2.2)	1	1 (1.5)	1	2 (5.6)	2
Pneumonia	0	…	1 (2.2)	1	0	…	1 (2.8)	1
Respiratory tract infection viral	0	…	1 (2.2)	1	0	…	0	…
Rotavirus infection	0	…	0	…	1 (1.5)	1	0	…
Sinusitis	0	…	0	…	2 (3.1)	2	1 (2.8)	1
Tinea versicolour	0	…	0	…	1 (1.5)	1	0	…
Urinary tract infection	0	…	3 (6.5)	5	0	…	0	…
Vaginal infection	0	…	0	…	1 (1.5)	1	0	…
Viral upper respiratory tract infection	0	…	0	…	2 (3.1)	2	0	…

AE=adverse event; AESI=adverse event of special interest; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per standard of care category; n=number of participants for whom the observation was reported; NSID=nonsteroidal immunosuppressive drug; PT=Preferred Term; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). a An AESI was defined as any AE in the MedDRA SOC Infections and infestations

rHuPH20

Clinical studies to investigate a possible interaction between rHuPH20 and efgartigimod have not been performed. SC-administered rHuPH20 is merely 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-113-2001 (efgartigimod PH20 SC and efgartigimod IV study) and ARGX-113-2002 (efgartigimod PH20 SC study), participants were allowed to receive vaccines that did not use live or live-attenuated biological material. Any inactivated subunit, polysaccharide, or conjugate vaccine was allowed at the discretion of the investigator and when administered at least 48 hours predose or 48 hours postdose of efgartigimod administration. In ARGX-113-1704 and ARGX-113-1705 (efgartigimod IV studies), vaccination of participants with live or live-attenuated vaccines was prohibited within 4 weeks of study entry, and vaccination with other vaccines was permitted 48 hours before or after an infusion.

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 efgartigimod PH20 SC injection.

The safety of immunization with live or live-attenuated vaccines and the response to immunization with vaccines are unknown. It is recommended to administer all vaccines according to national immunization guidelines and at least 4 weeks before initiation of treatment with efgartigimod. For participants who are being treated with efgartigimod, vaccination with live or live-attenuated vaccines is not recommended. For all other vaccines, vaccination should take place at least 2 weeks after the last administration of a treatment cycle and 4 weeks before initiating the next treatment cycle.

2.5.8.9. Discontinuation due to adverse events

Studies ARGX-113-2001 and ARGX-113-2002

A summary of AEs that resulted in IMP discontinuation in ARGX-113-2001 and ARGX-113-2002 is presented below.

Table 65: Studies ARGX-113-2001 and ARGX-113-2002: AEs Leading to Efgartigimod Discontinuation by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Study ARGX-113-2001				Study ARGX-113-2002							
					Antecedent study treatment assignment							
	EFG PH20 SC (N=55)		EFG IV (N=55)		SC 2001 (N=51)		IV 2001 (N=48)		IV 1705 (N=65)		Total (N=164)	
	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
≥1 AE leading to discontinuation of IMP	2 (3.6)	2	0	...	0	...	1 (2.1)	1	2 (3.1)	3	3 (1.8)[a]	4
Infections and infestations	1 (1.8)	1	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
COVID-19	1 (1.8)	1	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Renal cancer metastatic	0	...	0	...	0	...	1 (2.1)	1	0	...	1 (0.6)	1
Nervous system disorders	1 (1.8)	1	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Myasthenia gravis crisis	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Myasthenia gravis	1 (1.8)	1	0	...	0	...	0	...	0		0	
Respiratory, thoracic and mediastinal disorders	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1
Respiratory failure	0	...	0	...	0	...	0	...	1 (1.5)	1	1 (0.6)	1

AE=adverse event; CSR=clinical study report; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set per treatment; n=number of participants for whom the observation was reported; PT=Preferred Term; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021). The SC 2001 group refers to participants who received efgartigimod PH20 SC in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 2001 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-2001 and efgartigimod PH20 SC in extension study ARGX-113-2002. The IV 1705 group refers to participants who received efgartigimod IV in antecedent study ARGX-113-1705 and efgartigimod PH20 SC in extension study ARGX-113-2002. The total group refers to all participants who received efgartigimod PH20 SC in extension study ARGX-113-2002. a Two participants with fatal SAEs were included among the discontinued participants

SC Pooling Block

A summary of AEs that led to efgartigimod PH20 SC discontinuation in the total group in the SC PB is provided by SOC and PT below. The only AE that led to discontinuation that occurred in >1% of participants was *COVID-19*.

Table 66: SC Pooling Block: AEs Leading to Efgartigimod PH20 SC Discontinuation by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total (N=168)	
	n (%)	m
≥1 AE leading to discontinuation of IMP	5 (3.0)	6
Infections and infestations	2 (1.2)	2
COVID-19	2 (1.2)	2
Nervous system disorders	2 (1.2)	2
Myasthenia gravis	1 (0.6)	1
Myasthenia gravis crisis	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.6)	1
Renal cancer metastatic	1 (0.6)	1
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1
Respiratory failure	1 (0.6)	1

AE=adverse event; IMP=investigational medicinal product; m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PT=Preferred Term; SC=subcutaneous(ly); SOC=System Organ Class Note: AEs were coded using MedDRA version 24.1 (Sep 2021)

IV Pooling Block

A summary of AEs that led to efgartigimod discontinuation in the total efgartigimod group is provided by SOC and PT below. In the total efgartigimod group, 15 (9.1%) participants had AEs that led to efgartigimod discontinuation. In the total efgartigimod group, the only AE that led to efgartigimod discontinuation in >2 participants was Myasthenia gravis.

Table 67: IV Pooling Block: AEs Leading to Efgartigimod Discontinuation in the Total Efgartigimod Group by SOC and PT (Safety Analysis Set)

System organ class Preferred term	Total efgartigimod (N=164)	
	n (%)	m
≥1 AE leading to discontinuation of IMP	15 (9.1)	21
Nervous system disorders	7 (4.3)	10
Myasthenia gravis	5 (3.0)	5
Balance disorder	1 (0.6)	1
Cerebral venous sinus thrombosis	1 (0.6)	1
Facial paresis	1 (0.6)	1
Headache	1 (0.6)	1
Restless legs syndrome	1 (0.6)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.8)	3
Adenocarcinoma of colon	1 (0.6)	1
Lung neoplasm malignant	1 (0.6)	1
Rectal adenocarcinoma	1 (0.6)	1
Infections and infestations	2 (1.2)	2
COVID-19 pneumonia	2 (1.2)	2
Blood and lymphatic system disorders	1 (0.6)	1
Thrombocytosis	1 (0.6)	1
Cardiac disorders	1 (0.6)	1
Acute myocardial infarction	1 (0.6)	1
Gastrointestinal disorders	1 (0.6)	1
Irritable bowel syndrome	1 (0.6)	1
Injury, poisoning and procedural complications	1 (0.6)	1
Spinal compression fracture	1 (0.6)	1
Musculoskeletal and connective tissue disorders	1 (0.6)	1
Myalgia	1 (0.6)	1
Skin and subcutaneous tissue disorders	1 (0.6)	1
Rash	1 (0.6)	1

AE=adverse event; IV=intravenous(ly); m=number of events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of participants in the analysis set; n=number of participants for whom the observation was reported; PT=Preferred Term; SOC=System Organ Class

2.5.8.10. Post marketing experience

As of 31 Mar 2022, approximately 273 patients with gMG in the US have been treated with efgartigimod IV.

As of 31 Mar 2022, 72 ICSRs containing 187 events have been received for patients with gMG who were treated with efgartigimod IV. Of these ICSRs, 44 (23.5%) were solicited reports (from market research or patient support programs), 17 (9.1%) were spontaneously reported, and 11 (5.9%) were received from expanded access programs. A total of 33 patients were male and 33 patients were female (3 were unreported and 3 were unknown). The mean age was 61.5 years (range: 18-92 years; age was not reported for 17% of the patients).

Of the 187 events reported, 16 (8.6%) were serious (table below; all assessed as unlisted) and 171 (91.4%) were nonserious. Of the nonserious cases, 155 (90.6%) were unlisted and 16 (9.4%) were listed. Commonly reported AEs (≥3% by event count) included Fatigue (7%), Dyspnoea (4.8%), Headache (3.2%), and Diplopia (3.2%).

There were 3 fatal cases reported (all spontaneous) with a mean age of 73.3 years (range: 68-79 years). Limited information was available for the fatal cases, including the cause of death; therefore, no clinically meaningful conclusion can be drawn.

Overall, the AEs reported were consistent with the manifestation of the underlying MG disease or with the Adverse Drug Reactions (ADRs) described in the current efgartigimod IV USPI.

Table 68: SAEs in postmarketing data

Event Preferred Term	Source	Event outcome
Hypersensitivity	Compassionate use	Recovered
Diverticulitis Surgery	Compassionate use	Not recovered Not recovered
Death	Spontaneous	Fatal
Celulitis Fracture treatment	Spontaneous	Not reported Not reported
Tracheostomy malfunction	Spontaneous	Not reported
Confusional state Coagulopathy Chromaturia Dehydration	Solicited	Not reported
Death	Spontaneous	Fatal
Immobile	Solicited	Not reported
Dyspnoea Pulmonary oedema	Solicited	Unknown Unknown
Death	Spontaneous	Fatal

Source: Company global safety database
Note: The data cutoff data for postmarketing SAEs was 31 Mar 2022

2.5.9. Discussion on clinical safety

Safety data

The clinical safety database is based on three Phase 1 studies in healthy participants receiving efgartigimod SC with and without rHuPH20 (ARGX-113-1702, ARGX-113-1901 and ARGX-113-1907), two clinical studies in participants with gMG receiving efgartigimod PH20 SC (ARGX-113-2001 and ARGX-113-2002) and 3 clinical

studies in participants with gMG receiving efgartigimod IV (ARGX-113-1602, ARGX-113-1704 and ARGX-113-1705). The safety database was grouped into two pooling blocks (SC and IV pooling block). The two studies ARGX-113-2001 and ARGX-113-2002 as well as SC pooling block is used as the main clinical safety database. The IV studies and IV pooling block is used for comparisons to identify any clinically meaningful differences in the safety profile between efgartigimod alfa IV and efgartigimod PH20 SC and to support the long-term safety of efgartigimod PH20 SC. The MAH has presented the safety data for the overall population in the summary of clinical safety, including AChR-Ab seropositive and AChR-Ab seronegative participants, and states that the two populations safety profile and baseline characteristics are similar. The similar safety profile has been confirmed after the MAH presented the overall safety data on AChR-Ab seropositive patients and AChR-Ab seronegative patients side by side.

Study ARGX-113-2001: in the overall population (including AChR-Ab seropositive and negative participants), 55 participants were enrolled in the efgartigimod PH20 SC arm and 56 participants were enrolled in the efgartigimod IV arm (one patient didn't receive efgartigimod IV due to pyrexia). In the efgartigimod PH20 SC arm, 49 (89.1%) participants received all 4 doses. In the efgartigimod IV arm, 55 (100%) participants received all 4 doses. The MAH presented the reasons for the missing doses in the 6 participants in the efgartigimod PH20 SC arm. 3 participants had AEs (Covid-19 infection, myasthenia gravis and Injection site rash), 1 participant discontinued the study for personal reasons, 1 participant did not attend a visit for an unknown reason, and 1 participant was outside of the time window for administration.

Study ARGX-113-2002: A total of 178 participants rolled over to ARGX-113-2002 from ARGX-113-2001 and ARGX-113-1705. Of the 178 participants enrolled, 164 have received efgartigimod PH20 SC in the study and are defined as the total group. 14 of the 178 participants who rolled over to study ARGX-113-2002 did not receive efgartigimod PH20 SC at the time of the first interim analysis. Of these 14 participants, 3 participants discontinued the study (due to withdrawal of consent, lack of efficacy and screen failure). The 11 remaining participants had not yet received treatment according to the protocol.

SC pooling block: 168 participants received at least 1 dose of efgartigimod PH20 SC, including 55 in the "SC 2001" group and 113 in the "total IV" group, who rolled over from ARGX-113-2001 or ARGX-113-1705 to ARGX-113-2002.

A maximum of 6 cycles were started in participants in the SC PB: 168 (100%) participants with 1 cycle, 149 (88.7%) with 2 cycles, 117 (69.6%) with 3 cycles; 80 (47.6%) with 4 cycles, 38 (22.6%) with 5 cycles, and 8 (4.8%) with 6 cycles. A maximum of 5 cycles were completed in participants in the SC PB.

Overall, the duration of treatment combined with follow-up, for the total group, was at least 6 months for 104 (61.9%) participants. The mean (SD) duration of treatment combined with follow-up was 183.5 (67.25) days for the total group. The cumulative duration of treatment exposure was 84.4 total participant-years. There are no safety data on the efgartigimod PH20 SC for more than 12 months.

IV Pooling Block: A total of 164 participants received at least 1 dose of efgartigimod IV. A maximum of 19 cycles were started in participants in the IV PB. The mean (SD) duration of treatment combined with follow-up was 592.5 (291.86) days in the total efgartigimod group. Overall, the duration of treatment combined with follow-up was at least 12 months for 125 (76.2%) participants, at least 18 months for 105 (64.0%) participants, and at least 24 months for 63 (38.4%) participants.

Overall, the main safety database consisted of a total of 104 gMG patients treated with efgartigimod PH20 SC for at least 6 months and none patients treated with efgartigimod PH20 SC is for at least 12 months. To support the long-term safety of efgartigimod PH20 SC, the application relies on safety data from the efgartigimod PH20 SC, with support from safety data in the efgartigimod alfa IV, which is considered acceptable since the patient

population and active substance is the same. The efgartigimod alfa IV safety data adds 125 participants with at least 12-month exposure and 63 participants with at least 24 months exposure. There are limited data available on the use of efgartigimod beyond 2 years. As efgartigimod is intended to be used as a chronic therapy, long-term safety is included in the risk management plan (RMP) as missing information and further data will be collected on the safety of long-term treatment.

Adverse events

In study ARGX-113-2001, there were reported more AEs (67.3% vs. 50.9%), SAEs (14.5% vs 7.3%), Grade 3 or higher AEs (16.4% vs. 7.3%), Treatment related AEs (43.6% vs. 21.8%) and Procedure related AEs (25.5% vs. 3.6%) in the efgartigimod PH20 SC compared to the efgartigimod IV arm. Injection site reactions contributed to the higher frequency in the SC arm. In the extension study ARGX-113-2002, the reported AEs increased, probably due to longer exposure. However, when looking at the SC Pooling Block the frequency of participants with ≥1 AE in the total group decreased with each subsequent cycle. The frequencies in the IV pooling block is higher than in the SC pooling block, probably due to the longer exposure.

In study ARGX-113-2001, the most common reported AEs were Injection site rash (8 [14.5%] participants in the SC arm vs. 0 in the IV arm), Headache (7 [12.7%] participants each in both arms), Injection site erythema (7 [12.7%] participants in the SC arm and 0 in the IV arm), myasthenia gravis (6 [10.9%] participants in the SC arm and 1 [1.8%] in the IV arm). The MAH has added injection site reactions with the frequency "very common" to the ADR table in the SmPC section 4.8. This is endorsed.

In ARGX-113-2002, the most commonly reported AEs in were Injection site erythema, Headache, COVID-19, Injection site pain, Injection site pruritus, Injection site bruising, Diarrhoea, Injection site rash, Nasopharyngitis, and Injection site swelling. Headache and nasopharyngitis has previously been evaluated in the initial application for efgartigimod IV. Both AEs were reported in the same frequencies in the efgartigimod and placebo arm in study ARGX-113-1704 and therefore, not considered related to efgartigimod.

Overall, the type and frequency of commonly AEs were similar between those that occurred in the efgartigimod PH20 SC arm in ARGX-113-2001 and in the total group in ARGX-113-2002, except for diarrhoea, which were seen more frequently in the total group in ARGX-113-2002 (12 [7.3%] participants in the total group in ARGX-113-2002 vs. 1 [1.8%] participants in the SC arm in ARGX-113-2001). This is probably due to the longer time of exposure, since diarrhoea were seen in the same frequencies in the placebo group in study ARGX-113-1704.

The frequencies of the ADR table in the SmPC section 4.8 is based on data from the overall population as for the IV formulation. It is agreed that the overall gMG population is representative of the safety profile in AChR-Ab seropositive participants, and it is therefore acceptable to include the total population in the ADR table in 4.8.

Serious adverse events and Deaths, other significant events

Deaths

Two deaths were reported in participants who received efgartigimod PH20 SC. One participant with a history of renal cancer with no evidence of reoccurrence for >3 years at screening died because of an SAE of Renal cancer metastatic. One elderly participant with cardiovascular comorbidity died because of SAEs of COVID-19 and Respiratory failure.

In both cases the comorbidities have probably contributed to the outcome of death. However, 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.

Serious Adverse Events

8 (14.5%) participants had SAEs in the efgartigimod PH20 SC arm compared with 4 (7.3%) participants in the efgartigimod IV arm in study ARGX-113-2001. The most commonly reported SAE (≥5% of participants) was Myasthenia gravis which occurred in 5 (9.1%) participants in the efgartigimod PH20 SC arm and in 1 (1.8%) participant in the efgartigimod IV arm and thus contributed to the higher incidence of SAEs in the SC arm. None of the SAEs were considered by the investigator to be related to efgartigimod.

In study ARGX-113-2002, SAEs occurred in 17 (10.4%) participants in the total group. The most commonly reported SAEs (≥2 participants) were Myasthenia gravis (6 [3.7%]) participants), COVID-19 (3 [1.8%] participants), and Respiratory failure (2 [1.2%] participants). 1 SAE, a grade 3 Myasthenia gravis crisis event was considered related to efgartigimod PH20 SC.

Overall, the most frequent reported SAEs were myasthenia gravis and Covid-19. These AEs will be discussed further in the relevant sections below.

Adverse Events of Special Interest

AESIs occurred in 57 (33.9%) participants in the total group in the SC pooling block. The most frequently AESIs were COVID-19 (12.5%), Nasopharyngitis (6.5%), Upper respiratory tract infection (4.2%) and Pharyngitis (2.4%).

Serious AESIs occurred in 6 (3.6%) participants in the total group. Serious AESIs included COVID-19 in 3 (1.8%) participants. Cellulitis, COVID-19 pneumonia, Diarrhoea infectious, Pneumonia, and Rotavirus infection were reported in 1 (0.6%) participant each. The 3 severe cases of Covid-19 and the one death due to Covid-19 could be due to a compromised immune system however, considered the Covid-19 pandemic (high frequency) this cannot be confirmed. 'Serious infections' are included in the RMP as an important potential risk.

The total number of AESIs were highest in the group of nadir IgG category below the 25th quartile (45.0%) and lowest in the group with nadir IgG between the 50th percentile and 75th percentile (25.6%). The increase in the number of infections in the lowest IgG nadir quartile is consistent with the pharmacological action of efgartigimod. For Covid-19, no pattern was seen related to nadir IgG and equivalent to all other infections except for Nasopharyngitis, which were seen double as frequently in the nadir category below the 25th percentile compared to the other categories. The MAH states that 3 cases of Nasopharyngitis were assed to be related to treatment by the investigator. AEs of Nasopharyngitis were reported more frequently in the placebo arm (18.1%) than in the efgartigimod arm (11.9%) in ARGX-113-1704 and there was a similar rate per 100 PYFU in both the efgartigimod PH20 SC PB (15.4 per 100 PYFU) and the efgartigimod IV PB (13.9 per 100 PYFU), therefore Nasopharyngitis is not included in the ADR table in the SmPC.

The concomitant use of immunosuppressant treatments for gMG (e.g. steroids or NSIDs, or steroids + NSIDs) does not appear to affect the risk of infection.

In the IV pooling block, 101 (61.6%) participants in the total efgartigimod group had AESIs. The most frequent AESIs were Nasopharyngitis (17.1%), Urinary tract infection (11.6%), COVID-19 (11.0%), Upper respiratory tract infection (7.9%), Bronchitis (4.9%), and Herpes zoster (4.9%). Herpes zoster were discussed to be included in the ADR table in the SmPC 4.8 in the initial MAA for efgartigimod IV. Due to concomitant immunosuppressives in the infected participants and literature to support that FcRn is less likely associated

with increased infection risk or opportunistic infections when compared with steroids or other immunosuppressants, Herpes zoster is not included in the ADR table.

The total number of AESIs were slightly higher in groups of nadir IgG categories below the median than above the median. The small increase in the number of infections in the lowest 2 IgG nadir quartiles are consistent with the pharmacological action of efgartigimod. However, there was no temporal relationship between total IgG levels and severe infections in the clinical studies with efgartigimod. Based on the safety data reviewed, it is not considered necessary to monitor IgG levels or to change the treatment regimen based solely on IgG levels.

As shown in the SC pooling block, concomitant use of immunosuppressant treatments for gMG (e.g. steroids or NSIDs, or steroids + NSIDs) does not appear to affect the risk of infection.

Injection- and Infusion-Related Reactions

In the SC pooling block, 65 (38.7%) participants had injection-related reactions. Most injection-related reactions were localized Injection site reactions. All injection-related reactions were CTCAE grades 1 or 2, none were serious and there were no treatment discontinuations because of injection-related reactions. The most commonly occurring injection-related reactions were Injection site erythema (24.4%), Injection site pain (7.7%), Injection site rash (6.5%), and Injection site swelling (5.4%). This is expected in an SC administered antibody. A guidance on how to monitor for reactions and handle further treatments if an injection reaction occur has been added in the SmPC Section 4.2 and 4.4.

Further, a signal of anaphylactic reaction has been confirmed. Although this is based on data from the IV formulation only and it is noted that there are no cases of anaphylactic reaction reported from the development programme of the SC formulation, this ADR is also applicable to the SC formulation. The MAH has updated the SmPC section 4.2, 4.4 and 4.8 accordingly.

AEs of Myasthenia Gravis

In study ARGX-113-2001, 6 (10.9%) participants treated with efgartigimod PH20 SC and 1 (1.8%) participant treated with efgartigimod IV reported AEs of Myasthenia gravis. Overall, Myasthenia gravis was reported in 10 (6.0%) participants in the SC polling block and 8 (4.9%) participants in the IV pooling block. In the initial MAA for the IV formulation, Myasthenia gravis occurred with similar frequency in the efgartigimod arm and placebo arm and was therefore not considered related to efgartigimod. Further, myasthenia gravis crisis is a known risk associated with myasthenia gravis with a reported incidence of 15-20% of myasthenic patients experiencing myasthenic crisis at least once in their lives.

The 5 out of 6 events related to SC formulation occurred during the 7-week posttreatment follow-up period. 2 out of 6 receiving SC formulation had a bodyweight >90 kg. However, those 2 participants had events that are known triggers for MG exacerbations: administration of high dose steroids and infection, which correlated temporally with their MG exacerbation. Body weight related to SAEs is further discussed in the relevant section. 4 participants had moderate to severe gMG (MGFA Class III or IV) at screening.

In ARGX-113-2001, except for 1 seronegative participant, all participants who received all 4 efgartigimod administrations had reduced AChR-Ab levels at week 4 (−41% to −66% of baseline). For most participants who had a Myasthenia gravis AE, AChR-Ab levels started to increase after week 4, with values close to or above baseline at the time of the Myasthenia gravis AE. No specific factors (e.g. reduced IgG levels or MG-ADL) were identified that could be linked to the events of Myasthenia gravis or Myasthenia gravis crisis. Myasthenia gravis AEs occurred in participants with more predisposing factors for MG worsening (higher disease burden at baseline, more bulbar symptoms, and those with previous use of rescue therapies). The lower frequency of

Myasthenia gravis AEs in study ARGX-113-2002 indicate a lower frequency of Myasthenia gravis AEs with treatment cycles administered as appropriate per clinical evaluation and therefore the AEs and SAEs of myasthenia gravis is not considered to be due to lack of efficacy of SC administrated efgartigimod.

Laboratory findings

In study ARGX-113-2001, 5 (4.5%) participants had grade 3 clinical laboratory abnormalities of lymphocyte count decreased. Of the 5 participants 1 participant in the efgartigimod PH20 SC arm had an AE of Rhinitis. The investigator did not consider the event to be related to efgartigimod.

In study ARGX-113-2002, 13 (8.1%) participants had a clinical laboratory abnormality of lymphocyte count decreased: grade 3 in 12 (7.5%) participants, and grade 4 in 1 (0.6%) participant. Among them, 2 participants also had treatment-related PTs of Lymphocyte count decreased. 2 grade 1 upper respiratory tract infections were reported as related to efgartigimod SC administration. This is expected and not concerning as the events were grade 1.

In the IV pooling block, Grade 4 laboratory abnormalities were reported for lymphocyte count decreased in 2 (1.2%) participants and hypernatremia in 1 (0.6%) participant. None of the AEs reported for these 3 participants were associated with the grade 4 clinical laboratory abnormalities.

Grade 3 lymphocyte count decreased were reported in 19 (11.7%) participants. In the initial MAA, the MAH has provided data which do not indicate that there should be any relation between patients with 'Lymphocyte count decreased' and infections or infestations. In the efgartigimod PH20 SC submission, no additional participants in the IV PB had grade 3 or 4 lymphocyte count decreased laboratory abnormalities.

Grade 3 hypertriglyceridemia were reported in 6 (4.1%) participants and grade 3 cholesterol in 2 (1.4%) participants. No cardiovascular relevant AEs were related to the mentioned grade 3 laboratory values.

In ARGX-113-1704 cycles 1 and 2, no clinically meaningful increases in mean laboratory measurements of triglycerides, LDL cholesterol, or total cholesterol were found and the changes were similar compared to placebo. The same pattern was seen in ARGX-113-2001 when comparing efgartigimod IV and PH20 SC administration. In the efgartigimod clinical studies conducted to date, no clinically relevant mean increases over time in lipids have been observed when compared with placebo.

The MAH states that the observed increases in total cholesterol and LDL cholesterol with other FcRn inhibitors were paralleled by a reduction in albumin. Compared with other FcRn inhibitors, efgartigimod mechanistically inhibits the IgG-binding portion on FcRn in a manner that is not linked to a reduction in albumin levels and consequently does not affect lipid levels.

Lipid abnormalities are expected in patients with gMG, given the long-term treatment with corticosteroids and this is supported by the number of participants in efgartigimod clinical studies with abnormal lipid profiles at baseline. No sustained increase in lipid parameters was found after treatment with efgartigimod. The grade 3 increases seen in the clinical studies can be explained by concomitant corticoid therapy or clinically relevant medical history.

Vital signs

Overall, there were no notable changes from baseline in vital sign parameters (heart rate, systolic BP, and diastolic BP) in both studies and data were similar to the data shown in the initial MAA.

ECG abnormalities

Severe abnormalities in ECG evaluations in ARGX-113-2001 and ARGX-113-2002 were general low and no more events were seen compared to the IV arm.

Suicidality assessment

The suicidality assessment is in line with the suicidality assessment from the initial MAA for the IV formulation and does not raise any concerns regarding efgartigimod SC.

Safety in special populations

Age

More SAE's, AE of CTCAE severity grade ≥3 and AE leading to discontinuation were seen in participants ≥65 years than those 18 to <65 years and two deaths occurred in participants ≥65 years. However, treatment-related AE's were more frequent in participants 18 to <65 compared to participants ≥65 years. One serious AE were reported as treatment-related in the ≥65 year-group. AESIs were similar between the two groups.

Caution should be taken when interpreting the data due to small subgroups. Further, the elderly may overall have a higher frequency of co-morbidities, which will increase the risk of AEs not necessarily related to study treatment and overall the safety profile is considered similar in the two age groups.

Body Weight

Baseline body weight ranged from 42.0 to 150.2 kg for participants in the efgartigimod PH20 SC arm of ARGX-113-2001. The frequency of grade ≥3 AEs and SAEs in the two ≥100 kg body weight categories was higher than in the other weight categories (36.4% and 25.0% for ≥100 to <125 kg and ≥125 kg respectively, compared to 0% for <50 kg, 10.0% for ≥50 to <75 kg and 15.4% for ≥75 to <100 kg). Further, Myasthenia gravis exacerbation was reported in three patients in the ≥100 to <125 kg body weight category.

The post hoc analyses performed for AEs by baseline weight showed a higher frequency of grade ≥3 AEs and SAEs in the 100 to <125 kg body weight category. However, because the number of participants in each body weight category was small (n=22 in the 100 to <125 group), caution should be taken in making conclusions.

Data from the 3 participants, in the ≥100 to <125 kg body weight category, who had AEs of Myasthenia gravis show that other clinical factors (e.g. baseline disease severity, concurrent infection, SAE of Optic neuritis, recent MG exacerbations and the treatment free follow-up period), may have influenced the AEs of Myasthenia gravis in these participants.

The data presented does not raise concerns on the lack of efficacy in obese patients.

Seropositive and Seronegative

The MAH states that no trends or patterns were observed between the 2 participant populations that indicate a clinically meaningful difference in the safety profiles. The similar safety profile has been confirmed after the MAH presented the overall safety data on AChR-Ab seropositive patients and seronegative patients side by side.

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.

Markers of hepatic function were evaluated as potential covariates in the population PK/PD analysis. Albumin, total bilirubin, AST, ALP, and ALT did not influence any of the model parameters in the final population PK/PD model.

Renal Impairment

There haven't been any clinical studies of efgartigimod in participants with renal impairment.

The overall safety profile was similar between participants with normal renal function and those with mild renal impairment. The frequency of participants with SAEs, AEs grade ≥3, and AEs leading to discontinuation was higher in participants with mild renal impairment than those with normal renal function. However, caution should be taken due to small numbers in the subgroup (N=35).

Overall, it is agreed that mild renal impairment at baseline did not affect the overall safety profile of efgartigimod. Use in patients with moderate and severe renal impairment is included as missing information in the RMP.

Immunological events

For ADA against efgartigimod, both incidence and prevalence were higher in the efgartigimod SC arm compared to the IV arm (Incidence: 34.5% vs. 20.0%, prevalence: 45.5% vs. 27.3%). For Nab against efgartigimod the incidence and prevalence were similar (3.6%).

When looking at the integrated analyses, the highest ADA incidence was observed in the first treatment cycle and subsequently lower for each cycle. NAb were detected during the first cycle and not during subsequent cycles for the 2 participants who were classified as NAb positive.

Overall, AEs were reported in 67.3% of participants in the efgartigimod SC arm. These AEs occurred in 63.3% (19) of participants who were ADA negative, 83.3% (5) of participants with treatment-unaffected ADA, 66.7% (12) of participants with treatment-induced ADA, and 100% (1) of participants with treatment-boosted ADA.

Injection- or infusion-related reactions that occurred within 48 hours after administration and AEs of Injection site reaction that occurred any time after efgartigimod PH20 SC administration were evaluated for correlation with ADA against efgartigimod to determine whether these AEs were potentially immune related in ARGX-113-2001. There was no clear association or temporal relationship between the occurrence of these AEs and the presence of ADA against efgartigimod.

The incidence, and prevalence of Ab against rHuPH20 was 5.5% and 14.5% respectively. The incidence of Ab against rHuPH20 increased for each cycle. However, overall the incidence across all cycles were low (14.5%). Injection site reactions occurred in 18 (38.3%) participants who were negative for Ab against rHuPH20 and in 3 (60.0%) participants with treatment-unaffected Ab against rHuPH20. There were no injection site reactions in participants with treatment-induced or treatment-boosted Ab against rHuPH20. Most injection-related reactions were localized. All injection-related reactions were CTCAE grades 1 or 2, none were serious and there were no treatment discontinuations because of injection-related reactions.

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 and there was no clear association or temporal relationship between AEs and ADAs against efgartigimod.

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, since patients who need chronic

plasmapheresis, PE, IVIg or monoclonal antibodies for controlling symptoms were not allowed in the study. 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 Risk Management Plan as missing information.

NSIDs or steroids were allowed and were used in the study populations; therefore, any potential interaction is accounted for in the safety profile. Analysis of treatment-emergent AESIs by concurrent treatment for gMG with ST, NSID, or ST+NSID or without any of these concomitant medications identified no meaningful differences between these groups and hence, no clinically relevant interactions related to the safety of efgartigimod and use with stable background therapy allowed in the pivotal trial are identified.

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

In ARGX-113-2001, 2 (3.6%) participants in the efgartigimod PH20 SC arm had AEs leading to treatment discontinuation. Neither event was considered by the investigator to be related to efgartigimod. There were no events leading to treatment discontinuation in the efgartigimod IV arm.

In ARGX-113-2002, 3 participants discontinued because of AEs. One (0.6%) participant in the IV 1705 group had a grade 4 Myasthenia gravis crisis event. The other 2 participants discontinued from the study because of fatal SAEs.

Overall, AEs leading to discontinuations were low. The discontinuation data does not raise any new safety concerns.

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 and deaths due to limited data. No new concerns are raised for efgartigimod alfa IV.

2.5.10. Conclusions on clinical safety

The main safety database consisted of a total of 104 gMG patients treated with efgartigimod PH20 SC for at least 6 months and no patients were treated with efgartigimod PH20 SC beyond 12 months. The efgartigimod alfa IV safety data adds 125 participants with at least 12-month exposure and 63 participants with at least 24 months exposure. There are limited data available on the use of efgartigimod beyond 2 years. As efgartigimod is intended to be used as a chronic therapy, long-term safety is included in the RMP as missing information and further data will be collected on the safety of long-term treatment.

The available safety data from the clinical development program show that efgartigimod was generally well tolerated. More AEs were reported in the SC arm compared to the IV arm in study ARGX-113-2001. Injection site reactions contributed to the higher frequency in the SC arm. Moreover, in study ARGX-113-2001, more patients in the SC arm reported AEs of Myasthenia gravis compared to the IV arm. It is plausible, that the higher frequency could be due to the presence of predisposing factors together with the treatment-free follow up period of minimum 7 weeks in the clinical trial and a regular cycling administration likely could lower the frequency.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 69: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Serious infections Malignancies
Missing information	Use in pregnant women Effect on vaccination efficacy and the use of 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

2.6.2. Pharmacovigilance plan

Table 70: On-going 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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
ARGX-113-1705 Ongoing	To evaluate the long-term safety and tolerability of efgartigimod administered to patients with gMG. To collect additional safety data to supplement that from the randomized placebo-controlled study ARGX-113-1704	• Long-term safety of efgartigimod treatment • Serious infections	Protocol submission	29 June 2018
			Interim analysis 4	Q4 2022
			Final report	Q4 2023

Post-authorization safety study Planned	To characterize the risks and missing information outlined in this risk management plan and evaluate whether there are specific and/or unexpected patterns	• Long-term safety of efgartigimod treatment • Serious infections • Malignancies • Use in pregnant women • Effect on vaccination efficacy and the use of live/attenuated vaccines	Protocol submission	28 Nov 2022

2.6.3. Risk minimisation measures

Table 71: 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: • ARGX-113-1705 – Q4 2023 • PASS- Q1 2029
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- Q1 2029
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: • PASS - Q1 2029
Effect on vaccination efficacy and the use of 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 - Q1 2029
Use with monoclonal antibodies	Routine risk minimization measures: • SmPC section 4.5 • PL section 2 Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities:

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 - Q1 2029
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: • ARGX-113-1705 – Q4 2023 • PASS - Q1 2029
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: • PASS - Q1 2029

PASS=post-authorization safety study, Q4=fourth quarter, PL=package leaflet, SmPC=summary of product characteristics

2.6.4. Conclusion

The CHMP considered that the risk management plan version 2.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

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.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vyvgart 20 mg/ml concentrate for solution for infusion (PL Key safety messages section 1,2,4 5 and 6 Design/Layout section 1-6) and Hemlibra 30 mg/mL solution for injection (IFU steps 6 thru 17 Pictograms steps 1-28). The bridging report submitted by the MAH has been found acceptable. Both leaflets share an identical design, layout and writing style. Only differences between the two leaflets are due to different content describing different methods of administration and storage conditions.

2.8.2. Labelling exemptions

A request of translation exemption of the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the MAH and has been found acceptable by the QRD Group for the following reasons:

taking into consideration the orphan designation of the product, the small size of the outer carton, and in line with previous QRD conclusion applicable to the 20 mg/mL concentrate for solution for infusion, the proposed request to display the list of excipients in only one of the official EU languages on the multilingual packs of the 1000 mg solution for injection was deemed acceptable.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Generalized MG is a rare, chronic, neuromuscular autoimmune disease mediated by pathogenic IgG autoantibodies, binding to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane at the neuromuscular junction, which causes debilitating and potentially life-threatening muscle weakness.

MG is considered a model antibody-mediated autoimmune disease, since in most cases the autoantibodies and target antigens are well-characterised. MG pathogenesis, its clinical presentation and the response of patients to therapy vary depending on the pattern of autoantibodies detected. In general, treatment goals are to treat symptoms, to manage myasthenic exacerbations and to achieve minimal manifestation status.

3.1.2. Available therapies and unmet medical need

Current treatment options include acetylcholinesterase inhibitors, short-term immune therapies such as plasmapheresis or IVIG, and long-term immune therapies with immunosuppressive agents such as

corticosteroids, azathioprine, cyclosporine, and mycophenolate, but tacrolimus, methotrexate, and cyclophosphamide are also used. Thymectomy is also a treatment option. Monoclonal antibodies such as eculizumab or rituximab are used for more refractory cases. Efgartigimod IV and ravulizumab were approved in 2022 and this therapeutic area is expanding.

A considerable variation exists in the management of gMG. There is no consensus on the choice of immunosuppressive agent and widespread use of particular agents remains. With the exception of AChE inhibitors, azathioprine, the complement inhibitors eculizumab and ravulizumab, and the FcRn antagonist efgartigimod IV which have received regulatory approval for the treatment of gMG subgroups; other therapies are used off-label. Some therapies are associated with an increased risk of serious side effects or patient inconvenience, which may limit their use.

Patients with AChR-Ab seronegative gMG have greater limitations on approved treatment options, as AChE inhibitors are known to have reduced efficacy or cause worsening in this population and new treatments like C5 or FcRn inhibitors are approved only for AChR-Ab seropositive patients. On the other hand, some subgroups usually greatly benefit from PLEX in contrast to their reduced response to IVIG, and they have a very good response to the administration of rituximab, possibly more pronounced than the other MG subgroups.

3.1.3. Main clinical studies

To bridge the results of the placebo-controlled study ARGX-113-1704 (using efgartigimod IV) to the SC formulation, a phase 3 PD NI study, ARGX-113-2001, was conducted in participants with gMG. This randomized, open-label, parallel-group study evaluated the PD, PK, efficacy, safety, tolerability, and immunogenicity profiles of efgartigimod PH20 SC 1000 mg and efgartigimod IV 10 mg/kg, each administered weekly for a total of 4 administrations in 1 cycle. After completing ARGX-113-2001, participants had the option to roll over to ARGX-113-2002. PD NI and clinical endpoints are used to show therapeutic equivalence of SC and IV formulations.

In ARGX-113-2002, the long-term safety and efficacy of efgartigimod PH20 SC is being evaluated in participants who rolled over from either ARGX-113-2001 (in which they may have received efgartigimod IV or efgartigimod PH20 SC) or ARGX-113-1705 (in which all participants received efgartigimod IV). Subsequent cycles of efgartigimod PH20 SC were administered according to clinical evaluation. The frequency of treatment cycles may have varied by participant. This application includes data from the first interim analysis of ARGX-113-2002.

3.2. Favourable effects

The primary endpoint was met in study ARGX-113-2001. The LS mean estimate of the percent change from baseline in total IgG level at day 29 was -66.4% (95% CI: -68.91% to -63.86%) in the efgartigimod PH20 SC arm and -62.2% (95% CI: -64.66% to -59.71%) in the efgartigimod IV arm after 1 treatment cycle of 4 weekly administrations in participants with gMG. The corresponding LS mean difference in the percent change from baseline in total IgG levels at day 29 between the 2 arms (efgartigimod IV vs efgartigimod PH20 SC) was -4.2% (95% CI: -7.73% to -0.66%). Thus, the upper limit of the CI (-0.66%) was below the prespecified non-inferiority margin of 10%. Results for total IgG levels at day 29 were consistent when analysed for the AChR-Ab seropositive population in the mITT analysis set. The LS mean estimate of the percent change from baseline in total IgG level at day 29 was -66.9% (95% CI: -69.78% to -64.02%) in the efgartigimod PH20 SC arm and -62.4% (95% CI: -65.22% to -59.59%) in the efgartigimod IV arm.

Maximum mean percentage decreases in AChR-Ab levels of 62.2% (95% CI: -65.64% to -58.75%) and 59.7% (95% CI: -63.19% to -56.15%) were observed one week after the last administration in the efgartigimod SC and IV groups, respectively. The difference between arms was -2.5% (95% CI: -7.45% to 2.41).

For both the efgartigimod alfa SC and IV groups, decrease in total IgG and AChR-Ab levels were associated with and preceded a clinical response in AChR-Ab seropositive patients.

During first treatment cycle in the AChR-Ab seropositive population, the MG-ADL responder criterion (based on a reduction of ≥2 points from baseline on the MG-ADL score for ≥4 consecutive weeks) was met in 71.1% and 71.7% for participants in SC and IV arms, respectively (32 and 33 participants). The maximum reduction in MG-ADL total score was at week 4; the mean change from baseline at week 4 was −5.3 (0.42) versus −4.6 (0.38) ([95% CI: −1.83 to 0.41]) in SC and IV arms, respectively.

The percentage of QMG responders for the AChR-Ab seropositive population (based on a reduction of ≥3 points from baseline on the QMG score for ≥4 consecutive weeks) was 68.9% and 53.3% for participants in SC and IV arms, respectively. The maximum reduction in QMG total score was at week 4; the mean QMG change from baseline at week 4 was −6.5 (0.70) versus −5.4 (0.53) in SC and IV arms, respectively.

Sensitivity analyses on the possible impact due to treatment discontinuation, use of excluded concomitant medication or missed doses was done within the estimand frame, using imputation strategies for missing values based on missing at random assumption, as well as missing not at random. Based on this, it was concluded that the estimated treatment difference was very robust with very little impact due to these intercurrent events.

In study ARGX-113-2002, in the AChR-Ab seropositive population, the maximum MG-ADL total score reduction from cycle baseline decreased with subsequent cycles. The mean (SE) change from study baseline in MG-ADL total score in the total group at week 4 in the AChR-Ab seropositive population was −4.1 (0.29) in C1, −4.0 (0.32) in C2, −4.2 (0.35) in C3, and −4.6 (0.46) in C4.

3.3. Uncertainties and limitations about favourable effects

It is important to note that IV formulation has a weight-based dosing (10 mg/kg per infusion) up to 120kg, while SC formulation is a fixed dose for all weight ranges. However, weight-PD relationship is not established.

The primary endpoint cannot be accepted to show therapeutic equivalence of two formulations directly. The reduction of total IgG levels cannot be mechanistically linked to the disease, and the exposure-response relationship might be different for pathogenic antibodies. AChR-Ab levels (pathogenic IgG) are considered important for showing therapeutic equivalence in the AChR-Ab seropositive population but is not an approved PD biomarker for gMG.

There are no specific CHMP guidelines for myasthenia gravis therapeutic area or for demonstrating therapeutic equivalence in treatment of this population to support the choice of 10% NI margin. However, the issue is not pursued further as the data from ARGX-113-2001 is considered sufficiently compelling in terms of efficacy data and that requesting a more thorough justification of the relevance of the current NI margin as opposed to other choices is not considered of value.

With a NI margin of 10%-points in total IgG percent reduction, 84% (1–10/62.2×100%) of the PD effect was expected to be preserved. The model for NI margin predicted a loss of 3% to 4% clinical efficacy in terms of MG-ADL response, with a 10% less decrease in the average AUEC of percent IgG reduction between the baseline to week 4. In the worst-case scenario, on MG-ADL responder rate, the change of 95% CI for the difference of

IV-placebo (20.6% observed in ARGX-113-1704 Study) and the predicted SC-placebo would be around 3%. This treatment effect size is considered marginal but acceptable as a lower boundary.

The percentage of early MG-ADL responders was 62.2% vs 58.7% in the efgartigimod PH20 SC and IV arms, respectively. Early MG-ADL responder is defined as MG-ADL responder with onset of decrease occurring at the latest after the second administration of the IMP. Despite being promising for regular care of myasthenic patients, efgartigimod is not considered suitable to be used as a rescue treatment for myasthenic crisis, hence there is a warning in SmPC informing for treating physicians and class V patients were not enrolled in clinical studies.

Long term maintenance of effect for the SC formulation is unknown and is not tested beyond first cycle of treatment in a randomized controlled design. Maintenance of the effect is based on limited data from IV formulation and from study ARGX-113-2002 for up to 4 cycles with SC formulation. The number of patients treated are very low in longer term, so there are limitations to the maturity of data. For study ARGX-113-2002, exclusion of patients who did not respond to efgartigimod treatment or had life-threatening events during treatment limits the translation of the results to the future real-life experience. Only MG-ADL scores, not QMG, were collected in follow up study. Being aware of the limitations, the data is assessed as supportive evidence for maintenance of efficacy beyond first cycle with SC formulation.

During study ARGX-113-2001, although 54 out of 55 participants in SC arm completed the self-administration/ caregiver-supported administration training, only 42 (76.4%) were considered adequately trained for self-administration even after receiving up to 9 training visits. Afterwards, this situation did not improve much during open label follow up study. Although ARGX-113-2002 is a follow up study and a high dropout rate was observed, still only 31.3% of the administrations were performed by the participants/caregivers at home. Additional text regarding home administration has been added to section 4.2 of the SmPC in addition to guidance on the method of administration.

3.4. Unfavourable effects

In study ARGX-113-2001, there were reported more AEs (67.3% vs. 50.9%), SAEs (14.5% vs 7.3%), Grade 3 or higher AEs (16.4% vs. 7.3%), Treatment-related AEs (43.6% vs. 21.8%) and Procedure related AEs (25.5% vs. 3.6%) in the efgartigimod PH20 SC compared to the efgartigimod IV arm. The higher incidence of AEs, treatment- and procedure-related AEs in the efgartigimod PH20 SC arm compared with the efgartigimod IV arm is primarily due to injection site reactions (38.2% vs. 1.8%). Most injection-related reactions were localized injection site reactions. All injection-related reactions were CTCAE grades 1 or 2, none were serious and there were no treatment discontinuations because of injection-related reactions.

In study ARGX-113-2001, the most common reported AEs were injection site rash (8 [14.5%] participants in the SC arm vs. 0 in the IV arm), Headache (7 [12.7%] participants each in both arms), injection site erythema (7 [12.7%] participants in the SC arm and 0 in the IV arm) and myasthenia gravis (6 [10.9%] participants in the SC arm and 1 [1.8%] in the IV arm).

8 (14.5%) participants had SAEs in the efgartigimod PH20 SC arm compared with 4 (7.3%) participants in the efgartigimod IV arm in study ARGX-113-2001. The most commonly reported SAE (≥5% of participants) was Myasthenia gravis which occurred in 5 (9.1%) participants in the efgartigimod PH20 SC arm and in 1 (1.8%) participant in the efgartigimod IV arm and thus contributed to the higher incidence of SAEs in the SC arm. Overall, Myasthenia gravis was reported in 10 (6.0%) participants in the SC polling block and 8 (4.9%) participants in the IV pooling block. In the initial MAA for the IV formulation, myasthenia gravis occurred with

similar frequency in the efgartigimod arm and placebo arm and was therefore not considered related to efgartigimod. The 5 out of 6 events related to SC formulation occurred during the 7-week posttreatment follow-up period. It is considered plausible that higher frequency of myasthenia gravis exacerbations is due to the presence of predisposing factors together with the 7-week treatment free follow up period. Therefore, it is accepted not to include myasthenia Gravis exacerbation to the RMP as an important potential risk for the SC formulation.

The most frequently AESIs were COVID-19 (12.5%), Nasopharyngitis (6.5%), Upper respiratory tract infection (4.2%) and Pharyngitis (2.4%) in the SC pooling block. Serious AESIs occurred in 6 (3.6%) participants in the total group. Serious AESIs included COVID-19 in 3 (1.8%) participants. Cellulitis, COVID-19 pneumonia, Diarrhoea infectious, Pneumonia, and Rotavirus infection were reported in 1 (0.6%) participant each. The 3 severe cases of Covid-19 and the one death due to of Covid-19 could be due to a compromised immune system however, considered the Covid-19 pandemic (high frequency) this cannot be confirmed. 'Serious infections' are included in the RMP as an important potential risk.

For ADA against efgartigimod, both incidence and prevalence were higher in the efgartigimod SC arm compared to the IV arm (Incidence: 34.5% vs. 20.0%, prevalence: 45.5% vs. 27.3%). For NAb against efgartigimod the incidence and prevalence were similar (3.6%).

Further, a signal of anaphylactic reaction has been confirmed. Although this is based on data from the IV formulation only and it is noted that there are no cases of anaphylactic reaction reported from the development programme of the SC formulation, this ADR could also be applicable to the SC formulation.

In conclusion, AEs related to injections site reactions were the most frequently reported adverse event. Overall, these were localized and mild. Myasthenia gravis were reported more frequent in participants administered the SC formulation compared with the IV formulation and the events were serious. Most events occurred during the 7-week posttreatment follow up. Infections are a known safety concern for efgartigimod and serious infections is included in the RMP as an important potential risk.

3.5. Uncertainties and limitations about unfavourable effects

The main safety database consisted of a total of 104 gMG patients treated with efgartigimod PH20 SC for at least 6 months and no patients were treated with efgartigimod PH20 SC beyond 12 months. To support the long-term safety of efgartigimod PH20 SC, the application relies on short-term safety data from the efgartigimod PH20 SC, with support from safety data in the efgartigimod alfa IV, which is considered acceptable since the patient population and active substance is the same. The efgartigimod alfa IV safety data adds 125 participants with at least 12 months exposure and 63 participants with at least 24 months exposure. There are limited data available on the use of efgartigimod beyond 2 years. As efgartigimod is intended to be used as a chronic therapy, long-term safety is included in the RMP as missing information and further data will be collected on the safety of long-term treatment in a PASS.

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. The 3 severe cases of Covid-19 and the one death due to of Covid-19 could be due to a compromised immune system however, considered the Covid-19 pandemic (high

frequency) this cannot be confirmed. 'Serious infections' are included in the RMP as an important potential risk and will be addressed in a PASS.

Further missing data includes use in pregnant women, effect on vaccination efficacy and use of 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 MAA for the IV formulation and are also applicable to the SC formulation. They're all included in the RMP and will be addressed in a PASS.

3.6. Effects Table

Table 72: Effects Table for Efgartigimod SC 02.03.2022

Effect	Short Description	Unit	SC	IV	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint, IgG reduction, AChR+	Percent reduction from baseline in total IgG levels at day 29 (ie, 7 days after the fourth IV or SC administration)	LS (95% CI)	N=41 -66.9 (−69.78 to −64.02)	N=43 -62.4 (- 65.22 to −59.59)	10%-point reduction. AChR-Ab seropositive group should be used as the population for primary analysis. Total IgG reduction cannot be mechanistically linked to gMG.	(1)
			-4.5 (-8.53 to -0.46)		p<0.0001	
Post-hoc analysis, AChR-Ab levels, AChR+	Percent reduction from baseline in AChR-Ab levels at day 29 (ie, 7 days after the fourth IV or SC administration)	LS (95% CI)	N=44 -62.2 (-65.64 to -58.75)	N=42 -59.7 (-63.19 to -56.15)	10%-point reduction. Post-hoc analysis. Pathogenic IgG could be mechanistically linked to the disease. Large CI is a concern.	(1)
			-2.5 (-7.45 to 2.41)	p<0.0001		
MG-ADL responder, AChR+	participants with a reduction of ≥2 points from baseline on the MG-ADL score for ≥4 consecutive weeks occurring at latest 1 weeks after last IMP administration	n/N (%)	32/45 (71.1)	33/46 (71.7)	AChR-Ab seropositive group should be used as the population for clinical endpoint analysis	(1)

Effect	Short Description	Unit	SC	IV	Uncertainties/ Strength of evidence	References
QMG responder, AChR+	participants with a reduction of ≥3 points from baseline on the QMG score for ≥4 consecutive weeks occurring at the latest 1 week after last administration of IMP	n/N (%)	31/45 (68.9)	24/45 (53.3)	AChR-Ab seropositive group should be used as the population for clinical endpoint analysis	(1)
Unfavourable Effects						
Injection site rash	incidence	%	14.5	0		(1)
Injection site erythema	incidence	%	12.7	0		(1)
Injection site pruritus	incidence	%	9.1	0		(1)
Injection site bruising	incidence	%	7.3	0		(1)
Injection site pain	incidence	%	5.5	0		(1)
Myasthenia gravis	incidence	%	10.9	1.8		(1)
Myasthenia gravis	incidence	%	6.0		3 events in the ≥100 to <125 kg body weight category, it is currently unclear if the events could be due to lack of efficacy.	(2)
Myasthenia gravis	incidence	%		4.9		(3)
Headache	incidence	%	12.7	12.7		(1)
Covid-19	incidence	%	3.6	0		(1)
Pharyngitis	incidence	%	3.6	0		(1)
UTI	incidence	%	1.8	5.5		(1)
ADA against efgartigimod	incidence	%	34.5	20.0	Clinical impact of ADA is currently unclear.	(1)
ADA against efgartigimod	prevalence	%	45.5	27.3		(1)

Abbreviations: UTI: Urinary tract infections
Notes: (1) ARGX-113-2001, (2) SC pooling block, (3) IV pooling block

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study ARGX-113-2001 was conducted as a confirmatory trial and is acceptable for the purpose of showing "therapeutic equivalence" of the two formulations despite some uncertainties discussed below.

The clinical pharmacology of efgartigimod PH20 SC is documented in both healthy participants and patients with gMG. The primary PD endpoint in studies ARGX-113-1907 (healthy subjects) and ARGX-113-2001 (patients with gMG) was the percent reduction from baseline in total IgG levels at day 29 (10%-point NI margin). In addition, *post hoc* analysis of the percent reduction from baseline in AChR-Ab levels at day 29 was performed and was supportive of the primary analysis.

ARGX-113-2001 is considered the main study for this application (for SC administration), while data from ARGX-113-2002 is supportive for maintenance of effect or safety profile after the first cycle. In study ARGX-113-2001, the most important effects observed are similar percentages of MG-ADL and QMG responders with SC and IV formulations in AChR-Ab seropositive population. Efficacy if IV formulation has previously been demonstrated for at least 2 cycles in a double-blind placebo controlled pivotal study. A 2-point reduction in MG-ADL total score can be considered as clinically meaningful and this was achieved and maintained for both groups in the first cycle. A 3.5-point difference has been shown to correlate with clinically meaningful change in QMG and this had been achieved at week 4 but was not maintained until week 10. For a cyclic treatment driven by clinical need, the results are considered clinically significant.

In the light of clinical results, even if the NI margin of 10%-points is not considered directly acceptable, the comparable and significant decrease shown on AChR-Ab levels and total IgG levels for the AChR-Ab seropositive gMG population is acceptable with the SC formulation.

It is important to note that the IV formulation has a weight-based dosing (10 mg/kg per infusion) up to 120kg, while the SC formulation is a fixed 1000 mg dose for all weight ranges.

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 in patients with gMG is manageable. Overall, the main safety database consisted of a total of 104 gMG patients treated with efgartigimod PH20 SC for at least 6 months and no patients were treated with efgartigimod PH20 SC beyond 12 months. The efgartigimod alfa IV safety data adds 125 participants with at least 12-month exposure and 63 participants with at least 24 months exposure. There are limited data available on the use of efgartigimod beyond 2 years. As efgartigimod is intended to be used as a chronic therapy, long-term safety is included in the RMP as missing information and further data will be collected on the safety of long-term treatment.

The available safety data from the clinical development program show that efgartigimod was generally well tolerated. More AEs were reported in the SC arm compared to the IV arm in study ARGX-113-2001. Injection site reactions contributed to the higher frequency in the SC arm. Moreover, in study ARGX-113-2001, more patients in the SC arm reported AEs of Myasthenia gravis compared to the IV arm. It is plausible, that the higher frequency could be due to the presence of predisposing factors together with the treatment-free follow up period of minimum 7 weeks in the clinical trial and a regular cycling administration likely could lower the frequency.

3.7.2. Balance of benefits and risks

Overall, in study ARGX-113-2001, SC and IV efgartigimod formulations (as add-on to standard therapy) have demonstrated a similar and clinically relevant efficacy in treatment of AChR-Ab seropositive population in one treatment cycle, as rated by patients and physicians and by total IgG reduction at day 29. This was supported by results from study ARGX-113-2002 for up to 4 cycles.

Although primary PD and secondary clinical endpoints were met, the primary endpoint cannot be accepted to show therapeutic equivalence directly. The modelling approach is not acceptable as addressed in the PK section, however, the impact on data used for B/R analysis is considered insignificant. The totality of evidence can support therapeutic equivalence of IV and SC formulations of efgartigimod.

The justification of the NI margin, focusing the presentation of all data on AChR-Ab seropositive population, investigation of any impact of changing to fixed dose from weight-based approach on efficacy, feasibility of self-administration at home, guidance to the physician on selection of patients for switch or timing of switch, possibility to switch between formulations and its potential impact on efficacy or immunogenicity were discussed and clarified during the procedure.

In general, treatment with efgartigimod was well tolerated, with a low incidence of SAEs, severe AEs and AEs leading to treatment discontinuation. Five deaths were reported, but none of them were assessed by the investigator as related to efgartigimod treatment. Efgartigimod appears to be associated with a higher risk of infections, in particular, herpes viral infections and fungal 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 safety profile was similar between the SC and IV formulation. However, some differences were noted; more AEs were reported in the SC arm compared to the IV arm in study ARGX-113-2001 due to a higher frequency of Injection site reactions in the SC arm. Moreover, in study ARGX-113-2001, more patients in the SC arm reported AEs of Myasthenia gravis compared to the IV arm. It is plausible, that the higher frequency could be due to the presence of predisposing factors together with the treatment-free follow up period of minimum 7 weeks in the clinical trial and a regular cycling administration likely could lower the frequency.

3.8. Conclusions

The overall benefit/risk balance of Vyvgart SC is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

The CHMP by consensus is of the opinion that Vyvgart is not similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Vyvgart 1000 mg, solution for injection is favourable in the following indication(s):

Vyvgart is indicated as an add on to standard therapy for the treatment of adult patients with

generalised Myasthenia Gravis (gMG) who are anti acetylcholine receptor (AChR) antibody positive.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Vyvgart 1000 mg, solution for injection SC subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

5. Appendix

5.1. CHMP AR on similarity dated 14 September 2023